DESIGN AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL PATCHES OF TRAMADOL HYDROCHLORIDE

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Submitted by

NANDHAKUMARAN.S

(Register No: 26116008)

Under the Guidance of

Mr. K. SUNDARAMOORTHY, B.Sc., M.Pharm.,

Professor, Department of Pharmaceutics

ADHIPARASAKTHI COLLEGE OF PHARMACY

(ACCREDITED BY "NACC" WITH A CGPA OF 2.74 ON A FOUR POINT SCALE AT "B" GRADE)

MELMARUVATHUR - 603 319

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CERTIFICATE

This is to certify that the research work entitled "**DESIGN AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL PATCHES OF TRAMADOL HYDROCHLORIDE** '' submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **NANDHAKUMARAN .S (Register No. 26116008)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2012-2013.

Mr.K.SUNDARAMOORTHY, B.Sc., M.Pharm.,
Professor, Department of Pharmaceutics,
Adhiparasakthi College of Pharmacy,
Melmaruvathur - 603 319.

Place: Melmaruvathur
Date:

CERTIFICATE

This is to certify that the dissertation entitled **"DESIGN AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL PATCHES OF TRAMADOL HYDROCHLORIDE"** the confide research work carried out by **NANDHAKUMARAN. S (Register No. 26116008)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Mr.K.SUNDARAMOORTHY,** B.Sc., M.Pharm., Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, during the academic year 2012-2013.

Prof. (Dr.) T. VETRICHELVAN, M. Pharm., Ph.D.,
Principal,
Adhiparasakthi College of Pharmacy,
Melmaruvathur - 603 319.

Place: Melmaruvathur
Date:

Dedicated

To

My beloved

Family Members

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ABBREVIATIONS

CP 934P	---- Carbopol 934P
HPMC	---- Hydroxypropylmethylcellulose
Na CMC	---- Sodium Carboxymethylcellulose
SA	---- Sodium alginate
PVA	---- Polyvinyl alcohol
UV	---- Ultra Violet
µg	---- Microgram
λmax	---- Absorption maximum
ml	---- Millilitre
mg	---- Milligram
nm	---- Nanometer
FTIR	---- Fourier Transform Infra Red Spectroscopy
DSC	---- Differential Scanning Calorimetry
cm	---- Centimeter
%	---- Percentage
RH	---- Relative Humidity
I P	---- Indian Pharmacopoeia
t	---- Time
ICH	---- International Conference on Harmonization
w/v	---- weight/volume
gm	---- Grams
RPM	---- Revolutions per Minute
mm	---- Millimeter
S.No.	---- Serial Number
Fig	---- Figure
°C	---- Degree Celsius
GIT	---- Gastrointestinal Tract
SD	---- Standard Deviation
eg	---- Example
Eq	---- Equation
edn	---- Edition

INTRODUCTION...

1. INTRODUCTION

(Mathiowitz E., 2009)

Since the early 1980s there has been renewed interest in the use of bio adhesive polymers to prolong contact time in the various mucosal routes of drug administration.

The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability.

Drug absorption through a mucosal surface is efficient because mucosal surfaces are usually rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation by gastrointestinal enzymes and first pass hepatic metabolism.

1.1 Oral Trans mucosal Drug Delivery:

(Donald L.W., 2005; Chien Y. W., 2009; Robinson J.R., 2005)

Within the oral cavity delivery of drug is classified into the categories. Absorption of drug via mucous membranes of the oral cavity was noted as early as 1847 by Sobvero, the discoverer of nitroglycerin, and systemic studies of oral cavity absorption was first reported by Walton in 1935 and 1944.

Due to its excellent accessibility and reasonable patient compliance oral mucosal cavity offers attractive route of drug administration. Within the oral mucosal cavity delivery of drug is classified into three categories (I) Sublingual delivery which is a systemic delivery of drug through the mucosal membrane lining the floor of the mouth (ii) Buccal delivery & local delivery, for the

treatment of conditions of the oral cavity.

The oral cavity is foremost part of digestive system of human body. It is also referred to as "buccal cavity". It is accountable for various primary functions of body. The careful examination of various features of oral cavity can help in development of a suitable buccoadhesive drug delivery system.

1.2 ORAL CAVITY:

(Mathiowitz E., 2009; Rathbone M.J.et al., 1996; Vyas S.et al., 2002)

1.2.1Components or structural features of oral cavity:

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions.

- Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingiva (Gums).
- Oral cavity proper, which extends from teeth and gums back to the fauces (Which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

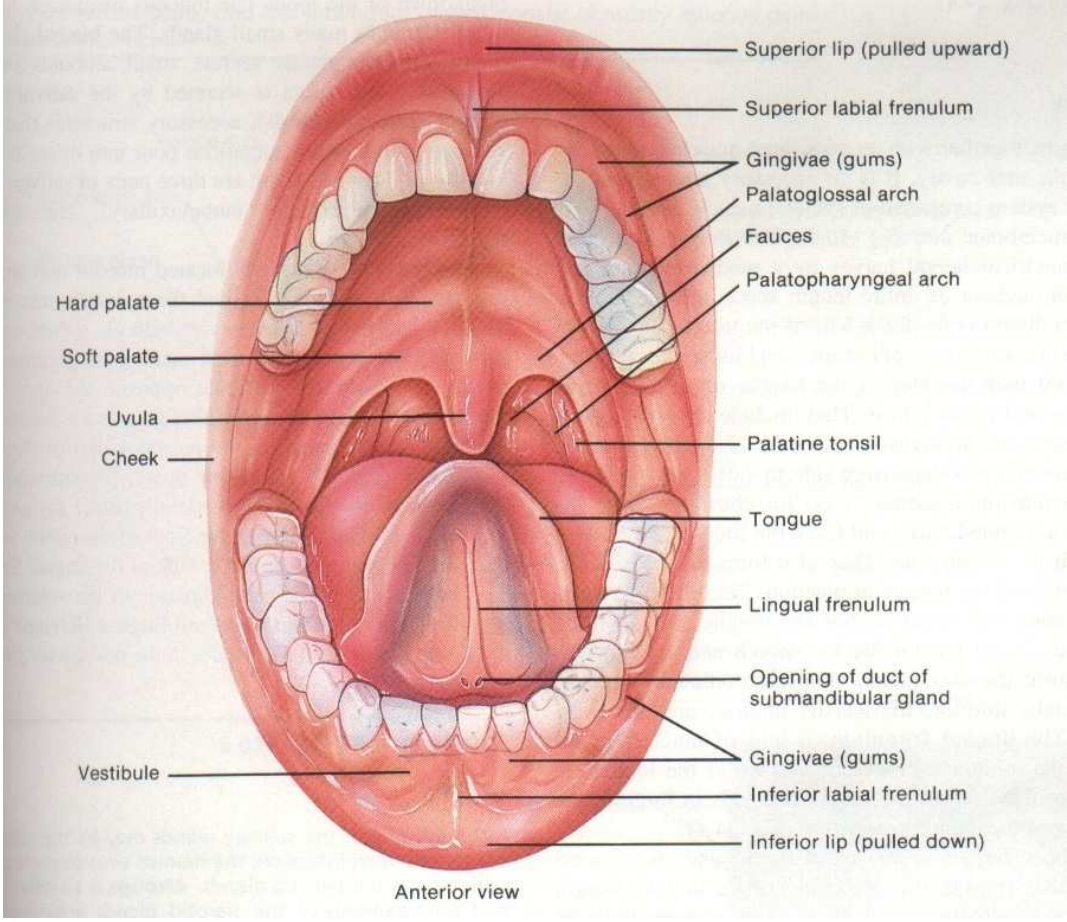


Figure-1.1: Structure of Oral Cavity

1.2.2 Anatomical Features:

The outer surface of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a submucousa containing blood vessels and nerves. The mucosa can be divided into three types:

- Masticatory mucosa, found on the gingiva and hard palate.
- Lining mucosa, found on the lips, cheeks, floor of mouth, undersurface of the tongue and the soft palate.
- Specialized mucosa found on the upper surface of the tongue and parts of the lips.

All consists of a squamous stratified epithelium, many cell layers (40-50 for buccal mucosa) overlying a connective tissue, layer, the lamina propria.

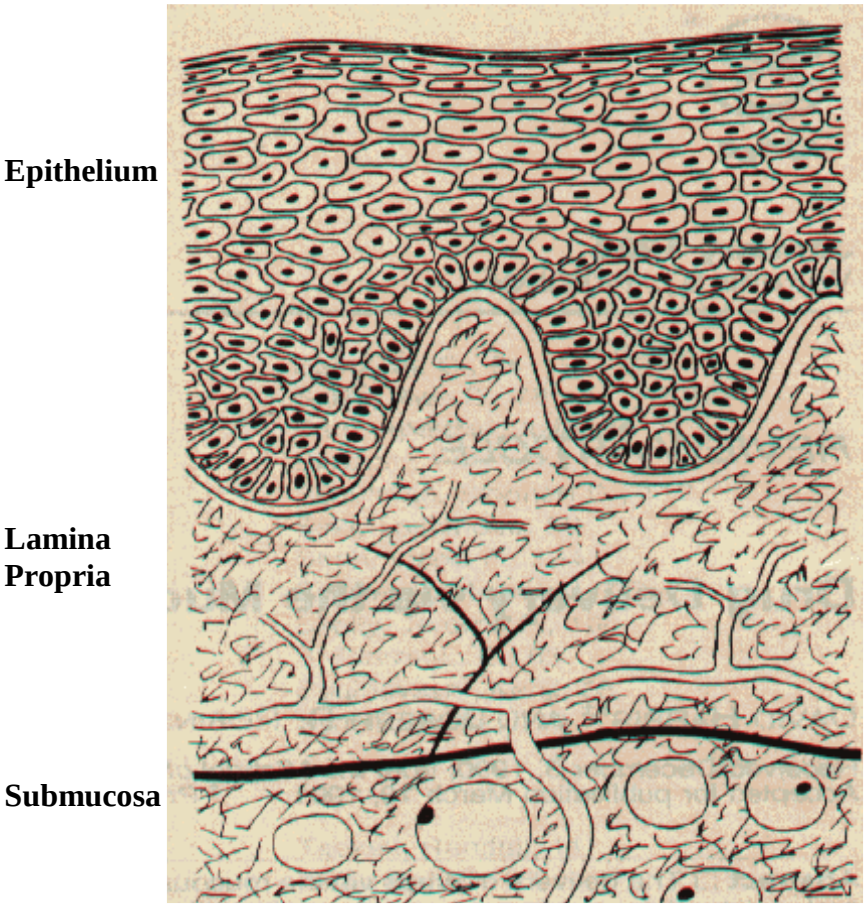


Figure-1.2: Structure of Buccal Mucosa

The total surface area of oral cavity= 170 cm^2.

Table-1.1: Thickness and surface area of oral cavity membranes

Oral cavity membrane	Thickness (mm)	Surface area (cm^2)
Buccal mucosa	500-600	5.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	--
Palatal	250	20.1

Intercellular connection in buccal tissue are characterized by desmosomes and tight junctions and the tissue is a somewhat leaky epithelium.The intercellular material between the superficial epithelial layers is extended by a unique organelle called "membrane coating granule". It has been shown In rat keratinized epithelium, that the lamella contents of the membrane-coating granules mix with existing material and form broad sheets in the intercellular spaces. These sheets are oriented parallel to the cell membrane and therefore may act as a barrier to permeability. Connective tissue papillae, which penetrate into the epithelia, give the basement membrane an enormous surface area compared to that of the surface of the epithelium.

1.2.3 Biochemistry of oral mucosa: **(***Rathbone M.J.et al., 1996.)*

All the layers of the oral mucosal membranes contain a large amount of protein in the form of ton filaments, consisting at least seven proteins called "keratins" with molecular sizes of 40-70 Kda. Keratinized and non- keratinized tissues of varying thickness and composition are found in oral cavity. Keratinized and non-keratinized tissue occupies about 50% and 30% respectively of the total surface area of the mouth. The difference between keratinized and non-keratinized

epithelia is merely the difference in the molecular size of existing keratins. Cells of non-keratinized epithelia contain lower molecular weight protein while those in keratinized epithelia contain mainly higher-molecular- weight keratins. The lipid content of the cells varies between tissues.

Table-1.2: Composition and state of keratinization of oral mucosa

Tissue	State of Keratinization	Composition
Buccal mucosa	Non-keratinized	Few neutral, but mainly polar lipids, particularly cholesterol sulfate and glucosylceramides
Sublingual mucosa	Non-keratinized	
Gingiva mucosa	Keratinized	Neutral lipids i.e., ceramides
Palatal mucosa	Keratinized	

1.2.4 Physiological aspects and functions of oral cavity:

The oral cavity is accountable for the following primary functions:

- As a portal for intake of food material and water.
- To bring chewing, mastication and mixing of food stuff.
- Lubrication of food material and formation of bolus.
- Identification of ingested material by taste buds of tongue.
- Initiation of carbohydrate and fat metabolism. Absorption of catabolic products thereafter metabolism.
- To aid in speech and breathing process.
- Slight antisepsis of ingested material and within oral cavity by saliva.

1.2.5 Secretions of Oral Cavity *(Mathiowitz E., 2009)*

The secretions in the oral cavity includes saliva, crevicular fluid and mucus.

1.2.5.1 Saliva:

Saliva is a complex fluid containing organic and inorganic materials. It is produced by the three pairs of major glands (parotid, submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity. The total average volume of saliva produced daily in an adult is around 750 ml. The flow rates of saliva depend upon the type of stimulus used, the time of day, the length of time glands had been stimulated, the age and sex of the individual and by their state of health. The average resting flow rate for whole saliva is 0.3 ml/ min (range 0.1-0.5 ml/min). For stimulated saliva the average flow rate is 1.7 ml/min (range 1.1 to 3.0 ml/min). Chemically, saliva is 99.5% water and 0.5% solutes. The solutes include ions (sodium, potassium, magnesium, phosphate, bicarbonate and chloride), dissolved gases, urea, uric acid, serum albumin, globulin, mucin and enzymes [lysozyme and amylase (ptyalin)].

The various physiological functions of saliva are:

- Modulation of oral flora.
- Remineralization of the teeth with calcium phosphate salts.
- Neutralization of acid in the oral cavity and esophagus.
- Lubrication and the cleansing of the oral, pharyngeal and esophageal mucosae.

- Assistance in bolus formation.
- Stimulation of epithelial proliferation.
- Initiation of fat and starch digestion.

The pH of whole saliva varies between 6.5 and 7.5. The main buffering system is the bicarbonate system; however, phosphate and protein buffers also play a minor role.

1.2.5.2 Crevicular Fluid:

It is a fluid secreted from the gingival glands of oral cavity.

1.2.5.3 Mucus:

Mucus is a thick secretion composed mainly of water, electrolytes and a mixture of several glycoproteins, which themselves are composed of large polysaccharides bound with smaller quantities of protein. It is secreted over many biological membranes of body for example, throughout the gastrointestinal tract walls. Mucus is secreted by special type of epithelia called mucosa. The mucus secreted in buccal cavity admixtures with saliva of salivary glands in oral cavity to produce whole saliva.

Mucus has two main functions:

- Protectant for biological membranes (exposed epithelia).
- Excellent lubricant.

The two main glycoprotein found in buccal mucus or mucin are MG1 and MG2. The mucin glycoprotein, MG1 consists of several disulphide-linked subunits containing a protein core with 4-16 oligosaccharide side-chain units. Its molecular

size is over 1000 KDa. A small mucin glycoprotein, MG2 has a molecular weight of 200-250 KDa and consists of a single peptide chain with 2-7 oligosaccharide side-chain units.

The important characteristics of mucus are:

- The glycoproteins of mucus have amphoteric properties and are therefore capable of buffering small amounts of either acids or alkalies.
- Mucus is strongly resistant to digestion by proteases.
- Mucus has adherent qualities that make it adhere tightly to the food or other particles and also to spread as a thin film over the surfaces.

The mucin film on the surface of oral mucosa provides the pharmaceutical scientist with the opportunity to retain delivery systems in contact with the mucosa for prolonged periods using mucoadhesives. This mucus, however, acts as potential barrier to drug penetration.

1.3 DRUG DELIVERY VIA ORAL CAVITY:

The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism, or for the administration of proteins and peptides. The two main-routes for administration with oral cavity are:

- Sublingual route
- Buccal route.

1.3.1 Drug Delivery via Sublingual Route:

Sublingual administration implies systemic administration of drugs via the membranes that line the floor of the mouth and ventral surface of the tongue. A rapidly dissolving tablet is generally given by the sublingual route. The sublingual routes offer some distinct advantages.

1. The sublingual mucosa is thinner than buccal mucosa and hence has comparatively higher permeability to drugs.
2. Rapid onset of action.
3. Quick termination of drug effect by spitting tablets.

Other advantages associated to this route are common to those of buccal absorption and discussed in later sections. The sublingual regions suffer with one major drawback. The two major salivary glands (submandibular and sublingual glands) open their ducts in sublingual area to release saliva. There is constant flushing of saliva in this region because of which it is difficult to retain drugs and delivery system and build or maintain high concentration of drug, in the sublingual region.

1.3.2 Drug delivery via buccal route:

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated in latter sections.

1.3.2.1 Terminology:

Various terms to be used in theoretical elucidation of buccal absorption are discussed below:

- Oral cavity mucosa: The membranes that line the oral cavity which include the sublingual, buccal mucosa, the gums (gingiva), the palatal mucosa and the labial mucosa.
- Buccal membrane: The membrane inside the mouth that lines the cheek.
- Buccal drug delivery system: A delivery system designed to deliver drugs systemically or locally via or to the buccal mucosa.
- Salivary pellicle: The components of saliva are adsorbed on to the surface of the oral mucosa to form a salivary pellicle. This pellicle coats all surfaces in the mouth and is a multilayered structure.

1.4 BUCCAL ABSORPTION: *(Bandyopadhyay A. K., 2008)*

Buccal administration involves systemic or local administration via or to the buccal membrane.

1.4.1 Mechanism:

Oral mucosal drug absorption occurs by passive diffusion of the non-ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. Beckett AH and his co-investigators showed using a variety of organic drugs from acids to bases, that the passive transfer of nonionic species across the lipid membrane of the buccal cavity was the primary transport mechanism. The buccal mucosa has been said to behave predominately as a lipoidal barrier to the passage of drugs; as is the case with many other mucosa and (within limits) the more lipophilic (or less ionized) the drug molecule, the more readily it is absorbed. It has been concluded that the passive diffuses in accordance with the pH partition theory of drug absorption is the major route of drug absorption for most drugs. However, it has been reported

that certain molecules e.g., some sugars and vitamins may be transported by a specialized transport system capable of saturation.

It has been proposed that the intercellular route, rather than the transcellular route, is the predominant route for drug absorption. Large hydrophilic molecules in particular are believed to be transported by the intercellular route and the presence of the contents of membrane-coating granules in the intercellular space may inhibit penetration in both keratinized and non-keratinized mucosae.

1.4.2 Dynamics:

The oral mucosal absorption of drugs could be adequately described by first order rate process. Several potential barriers to oral mucosa drug absorption have been identified. These include the mucus layer, keratinized layer, intercellular lipid of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply blood/lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. They proposed a linear relationship between salivary secretion and time thus: where ‘m’ and ‘C’ are the mass and concentration of drug in mouth at time ‘t’, Vi, the volume of solution put into mouth cavity and ‘V’ is salivary secretion rate.

T Suzuki et al designed a new perfusion system to study oral mucosal absorption drug using salicylic acid as a model drug in oral perfusion medium. They proposed following three compartment models.

C_p, drug concentration in plasma; Cm, drug concentration in perfusion medium; Ka, first-order absorption rate constant; F, fraction of disappeared drug transferred to circulating blood; K_{12} and K_{21}, first order transfer rate constants between two compartment K_{10} first order elimination rate constant: V_{dc} distribution volume of control compartment; V_{dt} distribution volume of peripheral compartment.

1.5 FACTORS AFFECTING BUCCAL ABSORPTION: *(Bhalodia R.et al., 2010)*

The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

1.5.1 Membrane Factors:

This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium; basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

1.5.2 Environmental Factors:

1.5.2.1 Saliva: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film effects buccal absorption.

1.5.2.2 Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

1.5.3 Movement of oral tissues:

Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods while withstanding tissue movements during talking and if possible during eating food or swallowing.

1.6 ADVANTAGES OF BUCCAL ABSORPTION: *(Bandyopadhyay A. K., 2008)*

The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation. Following buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect. Contact with the digestive fluids of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate.

The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, which may be advantageous if the drug delivery system or other excipients reversibly damage or irritate the mucosa. Additionally, there are two areas of buccal membranes per mouth, which would

allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.

There is good accessibility to the membranes that line the oral cavity which makes application painless and without discomfort, precise dosage form localization possible and facilitates ease of removal without significant associated pain and discomfort. Thus, patients can control the period of administration or terminate delivery in case of emergencies. The oral mucosal route has in the past exhibited better patient compliance than either the vaginal or rectal route of drug administration thus it would be anticipated that novel buccal dosage forms would be well accepted by patients. In addition, the route is not gender specific as is the case with vaginal route.

The oral mucosa is routinely exposed to a multitude of different foreign compounds and physical insult. So it has evolved a robust membrane that is less prone to irreversible damage by drug, dosage form or additives used therein. Thus, it may be feasible to include permeation enhancers in the formulation to increase systemic availability of the drug without observing permanent damaging effects.

Due to some therapeutic reasons oral cavity is the only ultimate route for drug delivery, for example, for those patients nil by-mouth, if either nausea or vomiting is a problem, if the patient is unconscious, in patients with an upper gastrointestinal tract disease or surgery, which affects gastrointestinal absorption or patient groups, which have difficulty in swallowing peroral medications e.g., very young and elderly.

Additional advantages of the oral cavity as a site for systemic drug delivery include: sterile techniques are not required during manufacture or administration, the oral cavity contains teeth upon which drug delivery systems can be physically attached using dental adhesives, the oral mucosa is low in enzyme activity and enzymatic degradation is relatively slow, hence, from the point of drug inactivation, the oral musocal route would be preferred to the nasal or rectal routes.

1.7 LIMITATIONS IN BUCCAL ABSORPTION:

(Bhalodia R.et al., 2010)

- The area of absorptive membrane is relatively smaller. If the effective area for absorption was dictated by the dimensions of a delivery system, this area then becomes even smaller.
- Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. In voluntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed.
- Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allerginicity and adverse properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route. In addition, the drug should not adversely effect the natural microbial flora of the oral cavity.
- Conventional type of buccal drug delivery systems did not allow the patient

to concurrently eat, drink or in some cases, talk.

- The permeability of the oral mucosa is not great compared to other mucosal membranes.

1.8 BUCCAL DOSAGE FORMS: *(Bhalodia R.et al., 2010)*

Buccal Dosage forms are meant to be placed between gingiva and cheek.

1.8.1 Conventional Dosage Form:

The conventional type of buccal dosage forms are buccal tablets, troches and lozenges, and mouth washers. Buccal tablets are small, flat, oval tablets and are intended to be held between the cheek and the teeth or in the cheek pouch (buccal tablets). Progesterone tablets can be administered this way. These tablets should be designed not to disintegrate but to slowly dissolve, typically over a 15 to 30 minutes period to provide for effective absorption. Troches and lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat. These tablet forms are commonly used to treat sore throat or to control coughing in common cold. Lozenges (pastiles or cough drops) are usually made with the drug incorporated in a flavored, hard-candy sugar base. Lozenges may be made by compression but are usually formed by fusion or by a candy – moulding process. Troches, on the other hand, are manufactured by compression as are other tablets. These two classes of tablets are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps 30 minute or less. A mouth wash is an aqueous solution, which is most often used for its deoderant, refreshing or antiseptic effect on buccal mucosa.

1.8.2 Advanced Buccal Dosage Forms:

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, tapes, semisolids (ointments and gels) and powders.

1.8.2.1 Mucoadhesive Tablets:

Buccal mucoadhesive tablets are dry dosage forms that move to be moistened prior to placing in contact with buccal mucosa. A double layer tablets, consisting of adhesive matrix layer of hydroxy propyl cellulose and poly (acrylic acid) with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate) has been described by Wagai. The two buccal adhesive tablets commercially available in UK are "buccastem" (Prochlor perazine maleale) and "Suscard Buccal" (glyceryl trinitrate).

1.8.2.2 Patches, Tapes & Films:

Buccal patches consists of two ply laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which was then cut to the required oval shape. A novel mucosal adhesive film called "Zilactin" – consisting of an alcoholic solution of hydroxy propyl cellulose and three organic acids, forms a film which applied to the oral mucosal surface which can be retained in place for at least 4 hours, even where challenged with fluids.

1.8.2.3 Semisolid Preparations (Ointments and Gels):

Bioadhesive gels or ointments have less patient acceptability than solid dosage adhesive forms, and most are used only for localized drug therapy within the oral cavity. One of the original oral mucosal-adhesive delivery systems

"orabase" consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes.

1.8.2.4 Powders:

Yam moto et al have described a hydroxpropyl cellulose and beclomethasone-diproprionate containing powder that was sprayed onto the oral mucosa of rats. A significant increase in the residence time relative to an oral solution was seen, and 2.5% of beclomethasone was retained on buccal mucosa for over 4 hours.

1.9 DESIGN OF BUCCAL MUCOADHESIVE PATCHES:

(Bandyopadhyay A. K., 2008; Mathiowitz E., 2009)

1.9.1 Different Components of Buccal Mucoadhesive Patches:

The different components of buccal mucoadhesive patches are as following:

- Drug
- Polymers (bio adhesive polymers, polymers controlling rate of release and polymers to prepare backing membrane).
- Backing membrane.
- Plasticizer
- Penetration enhancer.

1.9.2 Profile of Each component:

All the above ingredients are discussed in detail, as follows:

1.9.2.1 Drug:

The important drug properties that affect its diffusion through the patch as well as the buccal include molecular weight, chemical functionality and melting

point. The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on pharmacokinetic properties. Following are the critical properties for candidature to buccal mucoadhesive drug delivery.

- The conventional single dose of drug should be low.
- Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.The fraction of oral bioavailability F is low (F<0.5 in comparison to IV dose) and liver extraction ratio (ER) is high (ER>0.7).
- Drug absorption should be passive when given orally.
- The drug should not adversely affect the natural microbial flora or oral cavity.
- Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.
- The drug must be appreciably absorbed via buccal mucosa as evaluated by buccal absorption test.

1.9.2.2 Polymers: **(***Bandyopadhyay A. K., 2008)*

In buccal mucoadhesive patches, three different categories of polymers differing functionally are used. These are as follows:

- Bioadhesive polymers.
- Polymers controlling rate of release of drug from matrix.
- Polymers used to prepare backing membrane.

Each one of this will be discussed as follows:

1.9.2.3 Bioadhesive polymers: These are hydrophilic macromolecules that contain numerous hydrogen bond forming groups.These polymers become bio adhesive on hydration and are therefore called “wet adhesives”.

The characteristic properties of ideal bio adhesive are:

- It should have good mucoadhesive property and at the same time it should be innocuous to buccal mucosa.
- It should not chemically react with the drug and other excipients in Formulation.
- Molecular weight, glass transition temperature and chemical functionality of polymer must allow proper diffusion and release of drug.
- It should be pharmacologically bland-free from irritancy, allergenicity, bad taste and adverse properties such as discoloration or erosion of teeth. Cost of polymer should not be excessive.

Examples of good bio adhesive polymers include Hydroxy propyl cellulose (HPC), Hydroxy propyl methyl cellulose (HPMC), carbopol 934p, gelatin, pectin, PVP 44,000, sodium alginate, hydroxyethyl cellulose, PEG 6000, tragacanth, Gantrez-AN, methyl cellulose, carboxy methyl cellulose, sodium carboxy methylcellulose, Gantrez AN-139, starch, chitosan and diethylaminoethyl dextran.

1.9.2.4 Polymers controlling rate of releaseof drug from buccal mucoadhesive patches:

The polymers which are insoluble in saliva or water can be used as efficient matrix systems through which rate of release of drug can be controlled as desired. Examples for this category include ethylcellulose and butyl rubber. Water-soluble polymers can be used for controlling rate of release in which, rate of polymer dissolution will be release rate determining step.

1.9.2.5 Polymers used to prepare backing membrane:

The polymer whose solution can be casted into thin poreless uniform water impermeable film can be used to prepare backing membrane of patches. It should have good flexibility and high tensile strength and low water permeation. They should be stable on long storage maintaining their initial physical properties per se. The cellulose acetate in concentration of 2.4% w/v in acetone with 10% of plasticizer (PEG 4000 or glycerol) of total polymer weight when air dried produces a thin film suitable for backing membrane purpose. Similarly, 2-4% w/v solution of ethyl cellulose in 1:4 mixture of alcohol: toluene and suitable plasticizer can be casted into film.

The backing membrane can be of two types:

- A polymer solution casted into thin film. It is biodegradable in nature.
- A polyester laminated paper with polyethylene. It is not biodegradable.

The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for the backing membrane must be inert and impermeable to drugs and penetration enhancers. The thickness of the backing membrane must be thin and should be around 75-100 microns. The most commonly used backing materials are polyester laminated paper with polyethylene. Other examples include cellophane-325, multiphor sheet and polyglassine paper.

1.9.2.6 Plasticizer:

These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc. Usually the percentage of polymer falls in the range of 10-50% of total polymer weight. The plasticizers help in release of the drug substance from the polymer base as well as act as penetration enhancers. The choice of the plasticizer depends upon the ability of plasticizer material to solvate the polymer and alters the polymer – polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity.

1.9.2.7 Penetration Enhancers:

The use of penetration enhancers such as sodium lauryl sulphate, cetylpyridinium chloride, azone and capsaicin has been investigated as a suitable method for improving the penetration of non-peptide drugs through the buccal mucosa. Other effective penetration enhancers are sodium taurocholate, sodium deoxycholate, sodium methoxysalicylate, sodium dextransulphate and EDTA. Because all penetration enhancers perturb membrane integrity, it is inevitable that varying extents of insult will occur to the contacting membranes. Bile salts, laureth-9 and acylarnitines show a direct relationship between the degree of tissue damage and the extent of absorption promotion. In general, non-surfactant like enhancer appear to produce fewer morphological changes than their surfactant Counterparts.

1.10 Theories of Bioadhesion/ Mucoadhesion: *(Mathiowitz E., 2009)*

Mucoadhesion is proposed to occur in three stages. Initially, an intimate contact must form between the mucoadhesive and mucus (i.e., they must "wet" each other) then the mucus/ mucoadhesive macromolecules interpenetrate and finally the molecules interact with each other by secondary non-covalent bonds. The bonding occurs chiefly through both physical and chemical interactions. Physical or mechanical bonds result from entanglement of the adhesive material and the extended mucus chains. Secondary chemical bonds may be due to electrostatic interactions, hydrophonic interactions, hydrogen bonding and dispersion forces. Covalent bonding, such as Occurs with cyanoacrylates, is also possible for Mucoadhesion but is not yet common in pharmaceutical systems. Several theories of bioadhesion have been proposed to explain fundamental mechanism(s) of attachment. In a particular system one or more theories can equally well explain or contribute to the formation of bioadhesive bonds various theories propounded to explain mucoadhesion/ bioadhesion are:

- Wetting theory.
- Electronic theory
- Adsorption theory
- Diffusion theory
- Fracture theory.

1.10.1 Wetting Theory: This theory best describes the adhesion of liquid or paste to a biological surface. The work of adhesion can be expressed in terms of surface and interfacial tension (γ) being defined as the energy per cm^2 released when an interface is formed. According to Dupre's equation the work of adhesion is given by:

$$Wa = \gamma A + \gamma b - \gamma B \quad \ldots 1$$

Where the subscript A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by:

$$We = 2\gamma A = 2\gamma B \quad \ldots 2$$

For a bioadhesive material B spreading on a biological substrate A the spreading coefficient is given by:

$$S_{B/A} = \gamma A - (\gamma B + \gamma AB) \quad \ldots 3$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane. For a bioadhesive liquid B adhering to a biological membrane A the contact angle is given by:

$$\text{Cos } \varphi - (\gamma A - \gamma AB / \gamma B) \quad \ldots 4$$

1.10.2 Diffusion Theory:

Voyutski appears to be the first to discuss diffusion as a theory for adhesion. According to this theory the polymer chains and the mucus co-mingle to a sufficient depth to create a semi-permanent adhesive bond. The polymer chains penetrate the mucus; the exact depth to which it penetrates to achieve sufficient Mucoadhesion depends on diffusion coefficient, time of contact, and other experimental variables. The diffusion coefficient depends on molecular weight and decreases rapidly as the cross-linking density increases. The molecular weight, chain flexibility, expanded nature of the mucoadhesive and substrate as well as similarity in chemicals structure is required for good mucoadhesion.

1.10.3 Electronic theory:

According to this theory electron transfer occurs on contact of adhesive polymer and the mucus glycoprotein network because of difference in their electronic structure. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer. The electronic theory of adhesion was suggested by Derjaguin and Smigla.

1.10.4 Fracture Theory:

The fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by:

$$\sigma = \sqrt{\frac{E\varepsilon}{L}}$$

where E is young's modulus of elasticity, ε is the fracture energy and L is the critical crack length when two surfaces are separated. The work of fracture of an elastomer network Gc is given by:

$$Gc = \sqrt[K]{Mc}$$

K is a constant dependent on the density of the polymer, effective mass, length and flexibility of a single mucin chain bond and bond dissociation energy. Gc of an elastomeric network increases with molecular weight Me of the network stands.

1.10.5 Adsorption Theory:

Adsorption theory has been described by Kembell and Hantsherger. According to this theory after an initial contact of two surfaces the material will adhere because of surface forces acting between the atoms in the two surfaces.

Weak interaction of Vander Wall type plays an important role. However, if adsorption is due to chemical bonding i.e., chemisorption, then ionic, covalent and metallic bonds play an important role at the interface.

From a drug delivery point of view the mechanism of mucoadhesion appears best explained by a combination of diffusion and electronic theory, although other mechanisms may simultaneously be operative at minor level. It may also be more appropriate to restrict the term "mucoadhesion" to describing the adhesion of hydrated dosage forms to those mucus membranes having a substantial mucus layer. The term "bioadhesion" or "mucosal adhesion" may be more suitable to describe adhesion to the mucosal of the oral cavity.

1.11 FACTORS INFLUENCING BIOADHESION: (*Bandyopadhyay A. K., 2008)*

1.11.1 Physico-Chemical Parameters:

pH: pH influences the charge on the surface of both mucus and the polymer. The charge density of both mucus and the polymer are influenced by pH, which in turn affects mucoadhesion. Degree of hydration. Depending on the degree of hydration adhesion properties will be different. It is maximum at certain degree of hydration. When the degree of hydration is high, adhesiveness is lost probably due to formation of slippery, non-adhesive mucilage in an environment of a large amount of water at or near the interface.

1.11.2 Structural Properties:

1.11.2.1 Molecular weight and polymer chain length: High molecular weight polymers are generally preferred over low molecular polymers for mucoadhesion.

1.11.2.2 Spatial conformation: Despite a high molecular weight of 19,500,000 for dextrans they have similar adhesive strength to that of polyethylene glycol with a molecular weight 200,000. The helical conformation of dextran may shield any adhesively active groups, primarily responsible for adhesion, unlike PEG Polymers which have linear conformation.

1.11.2.3 Molecular flexibility: High molecular flexibility produces greater bioadhesion.

1.12.2.4 Chemical structure: Hydrogen bonding due to the presence of hydrophilic groups such as –COOH or –OH plays a significant role in mucoadhesion. The strongly anionic polyelectrolyte particularly those with a high charge density of –COOH or –OH functionality are better candidates for bioadhesion than neutral molecules.

LITERATURE SURVEY...

2. LITERATURE SURVEY

2.1. Literature Review:

Recent Advancements in Mucoadhesive Drug Delivery Systems:

Ananta Choudhury., et al. (2009) Designed a sustained release films of ciprofloxacin hydrochloride using different concentration of HPMC and PVA and evaluated for different parameters also *in-vitro* and *ex-vivo* drug release study, and release kinetic behavior. From the results concluded that all the prepared films having desire flexibility and mucoadhesive properties, good *in-vitro* and *ex-vivo* drug release performance. It was also concluded that in respect to mucoadhesion time, mucoadhesion strength study and *in-vitro* drug release study the performance of films composed of HPMC gives better results as compare to the films composed of PVA.

Attama AA., et al. (2008) Formulated novel buccoadhesive patches of hydrochlorothiazide using EC and HPMC by solvent casting method. The patches were evaluated for different parameters. The result of the study indicated that 1:2 ratios of EC and HPMC gave the highest buccoadhesive strength. The area swelling ratio indicated that the patches did not swell up to two times their initial areas, with the batch containing 3:2 ratios of EC and HPMC possessing the highest area swelling ratio. Higuchi analysis of the release mechanism indicated that the release of HCTZ from the patches formulated with 1:1 and 2:1 ratios of EC and HPMC predominantly occurred by a diffusion process.

Biswajit Basu., et al. (2010) Formulated mucoadhesive buccal patches of pimozide by using HPMC (15 and 47cps) carbopol 934, PVA, and PVP. The patches were evaluated for different parameters. The data of *in vitro* release from patches were fits into Hixon-Crowell, Higuchi and Korsmeyer-Peppas models. *In-vivo* studies in rabbits showed 85.97% of drug absorption from HPMC (15cps) patch in 60 min

Dhahrni S., et al. (2010) Design and evaluated mucoadhesive buccal patches of ondensetron HCl by solvent casting technique using HPMC-E15 as mucoadhesive polymer. The patches were evaluated for weight variation, thickness, surface pH, moisture absorption, *in-vitro* residence time, mechanical properties, *in-vitro* release, *ex-vivo* permeation studies and drug content uniformity and got the better results and obey first order kinetics.

Giradkar KP., et al. (2010) Deigned the polymeric films of tizanidine composed different proportions of NaCMC and CP 934 by solvent casting method, glycerol was used as plasticizer. Films were evaluated for different parameters It was concluded that NaCMC and CP-934(60:40) showed moderate drug release for 8 hrs. Increase in CP934 concentration resulted in decreasing the swelling index and surface pH. The mucoadhesive strength and *in-vitr*o residence time is slightly increased beyond 30%concentration of Carbopol 934.

Goudanavar PS., et al. (2010) Developed mucoadhesive buccal films of glibenclamide with HPC, PVP, and EC polymer combination, by solvent casting

technique and evaluated for number of parameters. The results revealed that the release of drug is depended on the polymer type as well as on their concentration. Film containing HPC alone released the maximum drug. Incorporation of PVP or EC reduced the release rate of Glibenclamide from the buccal film.

Koland ., et al. (2009) Formulated and evaluated fast dissolving films of ondensetron hydrochloride for sublingual administration by PVA, PVP, Carbopol-934 in different ratios, propylene glycol or PEG 400 as plasticizers and mannitol as sweeteners. Films evaluated for different parameters and bioadhesive strength. Concluded that use of water soluble sweeteners especially mannitol increases taste, also increases in drug release and drug permeation.

Manish., et al. (2010) Developed mucoadhesive buccal films of famotidine using HPMC, NaCMC and PVA by solvent casting method. The films were evaluated for their physical characteristics. Good results were obtained both *in-vitro* and *in-vivo* conditions for famotidine films. The results can be extrapolated to the human beings as the structure and permeability of buccal membrane of rabbits is similar to that of human beings. Hence the development of bioadhesive buccal formulations for famotidine may be a promising one as the dose of famotidine may be decreased and hence side effects may be reduced.

Nappinnai M., et al. (2008) Formulated buccal films of nitrendipine by using different polymers like HPMC K100, HPC, NaCMC, Sodium alginate, PVA, PVP K-30 and carbopol-934 were used. The films were evaluated for different parameters and *ex-vivo permeation*. From results, it was concluded that buccal films

of HPMC and NaCMC showed moderate drug release and satisfactory film characteristics, selected as best formulation.

Padmaja Chimmiri .,et al. (2012) were prepared Controlled released buccal films of Tramadol Hydrochloride and investigated using polymers HPMC K4M, sodium carboxy methyl cellulose, carbopol 934 in different ratios. Compatibility studies were done by using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry techniques (DSC). FTIR spectra and DSC thermograph of Tramadol Hydrochloride, polymers, and all formulations indicates that there is no chemical interaction and confirmed the stability of the drug. The films were evaluated for their physical characteristics like weight variation, Thickness, folding endurance, surface pH, drug content uniformity, swellingindex, Ex vivo bioadhesion time.

. ***Raghvendra Rao NG., et al. (2011)*** Buccal films of montelukast were prepared using mucoadhesive polymers like HPMC (K4M), HPMC (50cps), HPMC (5cps), Eudragit RL-100 and PVP K-30 by solvent casting technique, films were characterized for number of parameters and bursting strength, *in-vitro* drug release study. All formulations follow zero-order kinetics as (r^2) values are higher than that of first-order release kinetics. Mechanism of drug release pattern was confirmed by Higuchi plots.

Satishbabu BK., et al. (2008) Prepared bi laminated buccoadhesive film of atenolol, by solvent casting technique. The mucoadhesive layer was composed of mixture of drug and sodium alginate with or without carbopol-934P and backing layer was made of EC, and films were evaluated for different parameters. The

results show that bilaminated films were flexible and having suitable toughness. Also, sodium alginate was easily laminated on ethyl cellulose. The study concludes that the addition of carbopol-934P increases the viscosity and swelling of films, thereby control the release of drug and improves the mucoadhesive properties.

ShafiullahD., et al. (2006) Formulated mucoadhesive chlorhexidinebuccal films formulated films were evaluated for compatibility, drug content, antibacterial activity against Escherichia coli and *in-vitro* release studies. *In-vitro* release studies for films should a higher rate of drug release for HPMC films compared to chitosan films.

Shah Divyen., et al. (2010) Formulated mucoadhesive buccal films of lycopen using water soluble polymers by solvent casting technique, propylene glycol used as plasticizer. Films were evaluated for thickness, tensile strength, bending strength, film swelling and erosion properties, *ex-vivo* mucoadhesion time. It was concluded that formulation contains lower drug dose, sufficient for therapeutic effect, non-irritant, high mucoadhesion force and time required to dissolve is also high compare to other formulation.

Surya N. Ratha Adhikari., et al. (2010) were prepared Buccal patches for the delivery of atenolol using sodium alginate with various hydrophilic polymers like carbopol 934 P, sodium carboxymethyl cellulose, and hydroxypropyl methylcellulose in various proportions and combinations were fabricated by solvent casting technique. Various physico- mechanical parameters like weight variation, thickness, folding endurance, drug

content, moisture content, moisture absorption, and various ex vivo mucoadhesion parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated.

Thimmasetty J., et al. (2008) Prepared mucoadhesive buccal patches of carvedilol using the polymer such as HPMC, carbapol-934, eudragit RL 100 and ethyl cellulose. The formulated patches were evaluated for different parameters and in-vitro release studies were conducted for carvedilol loaded patches. Good results were obtained both in-vitro and in-vivo condition for carvedilol patches. The results can be extrapolated to the human beings as the structure and the permeability of buccal membrane of the rabbits is similar to that of human being.

Viram., et al. (2010) Formulated buccal films of carvedilol by using polymers like Eudragit RL-100, PVP, HPMC, NaCMC and Carbopol 934 in various combinations by solvent casting technique, using plasticizer propylene glycol with and without penetration enhancers like DMSO, Tween-60 and castor oil. In *ex-vivo* diffusion studies formulation were consisting DMSO which increase the drug permeability up to 15% given as the best formulation.

Vishnu M. Patel., et al. (2007) Designed mucoadhesive buccal patches containing propranolol hydrochloride using solvent casting method, by eudragit L-100, carbopol-934 and PVP K-30 polymers. Patches were evaluated for different parameters and ex-*vivo* mucoadhesive strength, *in-vitro* buccal permeation. Results indicates that the high amount of carbopol 934 and low amount of PVP K30 favour the *ex-vivo* mucoadhesive strength of the patches but low amount of carbopol

934 and high amount of PVP K30 favour the dissolution rate and swelling index of the patches.

Wong CF ., et al. (1999) Prepared controlled release buccal patches of metoprolol using eudragit incorporating HPMC, NaCMC and carbopol and were evaluated for various physical properties and drug release kinetics. Insoluble, flexible, organic solvent-free, controlled release patches could be fabricated using Eudragit NE 40D as the base matrix. The drug release as well as the adhesive properties of the patches could be modified by incorporating bioadhesive polymers. For the above purposes, Cekol 700 appeared to be the most suitable since it provided both satisfactory bioadhesion and a predictable rate of drug release.

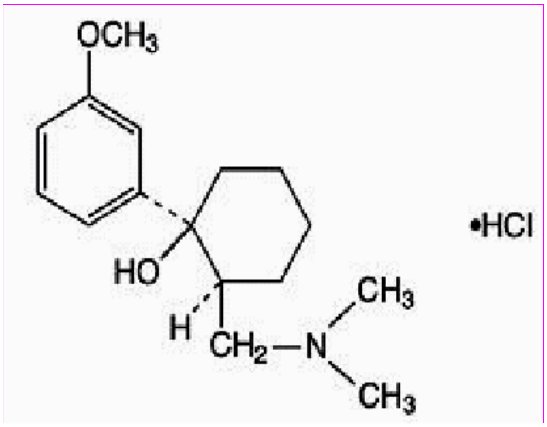
DRUG AND EXCIPIENTS

2.2 DRUG PROFILE: (www.rxlist.com/ Tramadol hydrochloride)

TRAMADOL HYDROCHLORIDE:

Chemically Tramadol hydrochloride is **2[(dimethyl amino) methyl]-1–(3–methyl phenyl) cyclohexane hydrochloride**. It is a steroidal drug and it contains not less than 99.00 % and not more than 101 % of $C_{21}H_{30}O_2$ calculated with reference to the dried substance

Structure:



Molecular Formula: $C_{16}H_{25}NO_2$

Molecular weight: 299.84

CHARACTERS:

Appearance:

White almost white, crystalline powder

Solubility:

Freely soluble in water, and methanol and practically insoluble in ethanol, acetone and in fatty oils.

Melting point:

180-184ºC.

Specific rotation:

+ 186 - +132, determined on a 1% solution in alcohol (95%).

PHARMACOKINETICS

Absorption:

Tramadol is almost completely absorbed. The bioavailability of a 100 mg dose is 75%. The peak plasma concentrations of racemic Tramadol occur 2 hours after the dose. The peak plasma concentrations of M1 occur 3 hours after the dose is given. Steady state is realized 2 days after dosing Tramadol four times a day. Food does not impact the rate or extent of absorption.

Half Life

The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum dosage of 400mg/day.

Distribution:

The volume of distribution was 2.6 L/kg in males and 2.9 L/kg in females. Tramadol binds to proteins about 20%. Saturation of plasma proteins is only of concern if one exceeds the recommended dosage.

Metabolic reactions:

Tramadol is extensively metabolised. The production of the only known active metabolite, M1 (mono-o-desmethylTramadol) is dependent on the CYP2D6 isoenzyme of the cytochrome P-450 enzyme system and hepatic impairment results in decreased metabolism of both the parent compound and the active metabolite. Patients who metabolise drugs poorly via CYP2D6 may obtain reduced benefit from Tramadol due to reduced formation of M1.

Excretion :

About 30% of Tramadol will be excreted in the urine unchanged. 60% of the drug will be excreted in the urine as metabolites. The rest is unidentified or is a metabolite which could not be extracted. Tramadol itself is eliminated via the liver. The half-life of Tramadol is 6.3 hours and the half-life of M1 is 7.4 hours. After repeated dosing of Tramadol, the half-life of Tramadol increased to about 7 hours.

Mechanism of action:

Tramadol is a new synthetic, centrally acting analgesic agent. The mechanism of action of Tramadol has yet to be fully elucidated, but it is believed to work through modulation of the gamma-aminobutyric acid (GABA)ergic, nor adrenergic and serotonergic systems. Tramadol, and its metabolite, known as M1, have been found to bind to μ-opioid receptors thus exerting their effect on GABAergic transmission, and to inhibit reuptake of 5-hydroxytryptamine (5-HT) and noradrenaline. The second mechanism is believed to be important since the analgesic effects of Tramadol are not fully antagonized by the μ-opioid receptor antagonist naloxone.

Uses:

Tramadol is used to treat moderate to moderately severe pain and most types of neuralgia, including trigeminal neuralgia. It has been suggested that Tramadol could be effective for alleviating symptoms of depression, anxiety, and phobias because of its action on the noradrenergic and serotonergic systems.

CONTRAINDICATION:

- Hypersensitivity to Tramadol or any of its components
- Hypersensitivity to opioids
- Patients acutely intoxicated with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs

Precautions:

- Acute abdominal conditions
- Renal impairment (caution with immediate-release, extended-release not recommended in severe renal impairment)
- Hepatic impairment (caution with immediate-release, extended-release not recommended)
- Respiratory depression
- Patients receiving anesthetic medications
- Patients who consume alcohol

Veterinary use:

Tramadol is used to treat post-operative, injury-related, and chronic (e.g., cancer- related) pain in dogs and cats as well as rabbits, coatis, many small mammals including rats and flying squirrels, guinea pigs, ferrets, and raccoons. Tramadol comes in ampoules in addition to the tablets, capsules, powder for reconstitution, and oral syrups and liquids; the fact that its characteristic taste is not very bitter and can be masked in food and diluted in water makes for a number of means of administration. No data that would lead to a definitive determination of the efficacy and safety of Tramadol in reptiles or amphibians is available at this time, and, following the pattern of all other

drugs, it Appears that Tramadol can be used to relieve pain in marsupials such as North American opossums, Short-Tailed Opossums, sugar gliders, wallabies, and kangaroos among others.

2.3 POLYMERPROFILE

2.3.1SODIUM ALGINATE *(Raymond C. Rowe., et al., 2003)*

Nonproprietary Names:

BP : Sodium Alginate

PhEur : Sodium Alginate

USP-NF : Sodium Alginate

Synonyms:

Alginatosodico; algin; alginic acid, sodium salt; E401; Kelcosol;Keltone; natriialginas; Protanal; sodium polymannuronate.

Chemical Name:

Sodium alginate

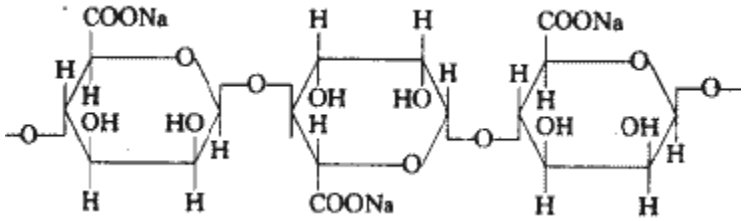
CAS Registry Number:

[9005-38-3]

Empirical Formula and Molecular Weight:

Sodium alginate consists chiefly of the sodium salt of alginicacid, which is a mixture of polyatomic acids composed of residues of Dmannuronicacid and L-guluronic acid.

Structural Formula:



Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrates;

Description

Sodium alginate occurs as an odorless and tasteless, white to paleyellowish-brown colored powder

Colour	**:**	pale yellowish-brown
Odour	**:**	odorless.
Taste	**:**	tasteless
Texture	**:**	powder
Acidity/alkalinity	**:**	pH _ 7.2 (1% w/v aqueous solution)

Solubility:

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

Stability and Storage Conditions:

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature. Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous

solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for2 years. Solutions should not be stored in metal containers. Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity. Solutions are ideally sterilized using ethylene oxide, although filtration using a 0.45 mm filter also has only a slight adverse effect on solution viscosity. Heating sodium alginate solutions to temperatures above 70°Ccauses de polymerization with a subsequent loss of viscosity. Autoclaving of solutions can cause a decrease in viscosity, which may vary depending upon the nature of any other substances present. Gamma irradiation should not be used to sterilize sodium alginate solutions since this process severely reduces solution viscosity. Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol, or parabens. If the medium is acidic, benzoic acid may also be used .The bulk material should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenyl mercuric acetate and nitrate, calcium salts, heavymetals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

Applications in Pharmaceutical Formulation or Technology:

1. Sodium alginate is used in a variety of oral and topical pharmaceutical formulations.

2. In tablet formulations, sodium alginate may be used as both a binder and disintegrates ;(3) it has been used as a diluent in capsule formulations.
3. Sodium alginate hasal so been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules and aqueous suspensions.
4. The effects of particle size, viscosity and chemical composition of sodium alginate on drug release from matrix tablets have been described.
5. In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions.
6. Recently, sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic solvent systems. It has also been used in the formation of nanoparticles
7. Sodium alginate is also used in cosmetics and food products; see table 2.1

Table 2.1: Uses of sodium alginate

USE	CONCENTRATION (%)
Pastes and creams	5-10
Stabilizer in emulsions	1-3
Suspending agent	1-5
Tablet binder	1-3
Tablet disintigrent	2.5-10

2.3.2HYPROMELLOSE (HYDROXYPROPYL METHYLCELLULOSE)

(Raymond C. Rowe, et al., 2003)

1. Nonproprietary Names

BP : Hypromellose

JP : Hydroxy propyl methylcellulose

PhEur : Hypromellosum

USP : Hypromellose

2. Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxy propyl cellulose; Metolose; Tylopur.

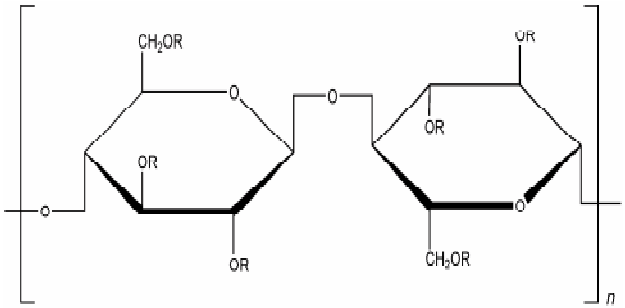
3. Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4. Molecular Weight

10,000 – 1,500,000.

5. Structural Formula



Where R is H, CH_3, or CH_3CH (OH) CH_2

6. Functional Category

Coating agent, film-former, rate-controlling polymer for sustained release, Stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, Hypromellose is primarily used as a tablet binder, in film- coating, and as matrix for use in extended-release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. Hypromellose at concentrations 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Lower-viscosity grades are used in aqueous film- coating solutions, while higher-viscosity grades are used with organic solvents.

8. Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

9. Typical Properties

Acidity/alkalinity	**:**	pH = 5.5–8.0 for a 1% w/w aqueous solution.
Density (bulk)	**:**	0.341 g/cm^3
Density (tapped)	**:**	0.557 g/cm^3
Density (true)	**:**	1.326 g/cm^3
Melting Point	**:**	browns at 190 – 200°C; chars at 225 230°C

Table :2.2 Various grades of hypromellose

Methocel product	USP 28 designation	Nominal viscosity (mPa s)
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

Solubility

It is soluble in cold water and forming a viscous colloidal solution, practically insoluble in chloroform and ethanol (95%) and ether. But it was soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol.

Viscosity (dynamic)

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.

10. Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively.

11. Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, Hypromellose will not complex with metallic salts.

2.3.3 Carbopol 934 *(Raymond C. Rowe, et al., 2003)*

Carbopol-934, a synthetic high molecular weight, non-linear polymer of acrylic acid cross-linked with polyalkenyl polyether with average molecular weight 3x106 Daltons. It contains not less than 56% and not more than 68% of carboxylic acid (-COOH) groups.

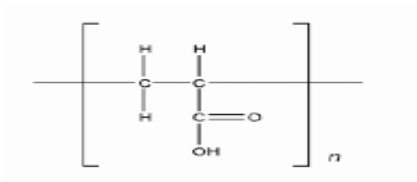
Synonym : Acritamer, acrylic acid polymer carboxy vinyl polymer.

Non proprietary names : BP carbomer, USP carbomer

Chemical name : Carboxyl polymethylene

Empirical formula : $(C_3H_4O_2)_x$ ($-C_3H_5$-sucrose)$_y$

Structure:



Category: Bioadhesive, emulsifying, suspending & viscosity enhancing agent, tablet binder and release-modifying agent.

Description: White, fluffy, acidic, hygroscopic powder with a slight Characteristic odour.

Solubility: After neutralization with alkali hydroxides or amines, soluble in water, in ethanol (96%) and in glycerol.

pH: 2.5-3.0 (1% aqueous solution)

Glass transition temp: 100–105°C

Melting point: decomposition occurs within 30 minutes at 260°C.

Specific gravity: 1.41

Viscosity: Carbomers disappears in water to form acidic colloidal solutions of low viscosity which when neutralized produce highly viscous gels. 29,400 to 39,400 cps at 25^{o}C (0.5% neutralized aqueous solution)

Stability and storage:

Carbomers are stable, though hygroscopoic materials and can be heated at temperatures below 104º for up to 2 hours without affecting their thickening efficiency.

Applications:

It is used as thickening, emulsifying and gelling agent. It is used as a tablet binder and matrix forming agent in sustained-release formulations affording zero- to near-zero-order release. It is used as the bioadhesive component in mucoadhesive ointments, gels and tablets.

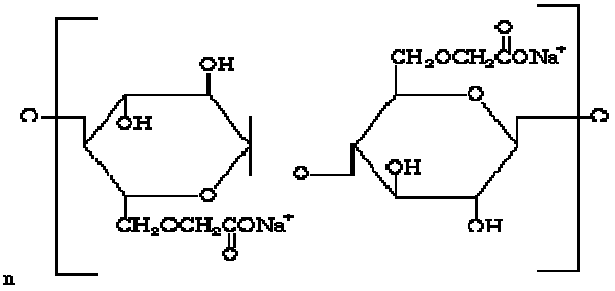
Safety:

Carbomers are regarded as non toxic and non-irritant.

2.3.4 CARBOXYMETHYLCELLULOSE SODIUM:

(Raymond C. Rowe,etal., 2003)

1. **Nonproprietary Names :** BP : Carmellose sodium
   USP : Carboxy methylcellulose sodium.
2. **Synonyms :** Akucell, Aquasorb, Balnose, Cellulose gum, CMC sodium, E466, Finn fix, Nymcel, SCMC, Sodium carboxy methylcellulose, Sodium cellulose glycolate, Sodium CMC, Tylose CB.
3. **Chemical Name :** Cellulose, carboxy methyl ether, sodium salt.
4. **Molecular weight :** Molecular weight is 90000-700000.
5. **Structural Formula :**



6. Functional Category:

Coating agent, stabilizing agent, suspending agent, Tablet and capsule disintegrates.Tablet binder, Viscosity increasing agent, Water-absorbing agent.

7. Applications in pharmaceutical formulation or technology:

- Carboxy methylcellulose sodium is widely used in oral and topical properties.
- Higher concentrations, usually 3-6%, of the medium-viscosity grades are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out.

Table2.3 Uses of carboxy methylcellulose sodium

Use	Concentration (%)
Emulsifying agent	0.25 – 1.0
Gel-forming agent	3.0 – 6.0
Injections	0.05 – 0.75
Oral solutions	0.1 – 1.0
Table binder	1.0 – 6.0

8. Description : Carboxy methylcellulose sodium occurs as a white to almost white, odorless, granular powder.

9. Typical properties :

- Density (bulk): 0.52 g/cm^3
- Density (tapped): 0.78 g/cm^3
- Dissociation constant: pK_a = 4.30

2.4EXCIPIENT PROFILE:

2.4.1 Polyvinyl Alcohol: *(Raymond C. Rowe, et al., 2003)*

Non Proprietory Name:

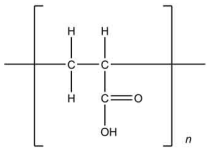
USP : Polyvinyl alcohol

Synonyms : Airvol, Elvanol, Vinyl alcohol polymer.

Chemical name and CAS Registry Number : Ethanol, homopolymer (9002-89-5).

Molecular weight : 30000-200000.

Structural formula :



Functional category:

Coating agent, non-ionic surfactant; viscosity – increasing agent.

Description:

PVA occurs as an odorless, white to cream colored granular powder.

Typical Properties:

- Acidity / alkalinity.
- pH 5.0 – 8.0 (4% aqueous solution).

Solubility:

Soluble in hot or cold water, solubility in water increases as the molecular weight decreases PVA is practically insoluble in aliphatic, aromatic and chlorinated hydrocarbons, esters, ketones and oils.

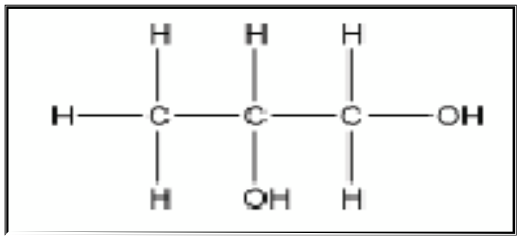
2.4.2 Propylene Glycol: *(Raymond C. Rowe, et al., 2003)*

Nonproprietary

Names:

BP	:	Propylene glycol
JP	:	Propylene glycol
PhEur	:	Propylenglycolum
USP	:	Propylene glycol
Synonyms	**:**	1, 2Dihydroxypropane
Empirical Formula	**:**	$C_3H_8O_2$
Molecular Weight	**:**	76.09

Structural Formula:



Functional Category:

Antimicrobial preservative, disinfectant, humectant, plasticizer, solvent, Stabilizer for vitamins, water-miscible cosolvent.

Description :

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

Typical properties:

- **Autoignition temperature:** 371°C
- **Boiling point:** 188°C
- **Density:** 1.038 g/cm3 at 20°C
- **Viscosity (dynamic):** 58.1 mPa s (58.1 cP) at 20°C.

Solubility:

Miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Stability and Storage Conditions:

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propion-aldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving.

Incompatibilities:

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

Safety:

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material. Propylene glycol is rapidly absorbed from the gastrointestinal tract; there is also evidence that it is absorbed topically when applied to damaged skin. In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin.

Applications in Pharmaceutical Formulation:

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

Aim And Objective....

3. AIM AND OBJECTIVES

The buccal route as an alternative to other traditional method of systemic drug administration is a subject of growing interest because of numerous advantages. It is well known that the absorption of therapeutic compound from the oral mucosa provide a direct entry of the drug into the systemic circulation, `therefore avoiding the first pass hepatic metabolism and gastrointestinal drug degradation which is associated with oral administration. The oral cavity is easily accessible for self-medication and hence it is well accepted by patient, and it is safe since the device can be easily administered and even removed from the site of application, stopping the input of drug whenever desired.

Drug like Tramadol hydrochloride has been selected as model drug because the drug has all the pharmacokinetics and physico-chemical properties required for controlled release. Tramadol hydrochloride has oral bioavailability 68 – 72 % and having elimination half-life of 5.5 - 7 hrs and having volume of distribution 2.6 L/kg in male 2.9 L/kg in female. The Tramadol hydrochloride is freely soluble in water.

Therefore, in the present study an attempt will be made to formulate buccal dosage form of Tramadol hydrochloride using different polymers and an adjuvants to avoid hepatic first pass metabolism.

The main objective of the present investigation was the following:

- To formulate buccal patches of Tramadol hydrochloride using various polymers like sodium alginate, hydroxy propyl methylcellulose, sodium carboxy methyl cellulose and carbapol 934.
- To study the influence of drug polymer ratio on drug release
- To evaluate the patches for their physical parameters like appearance, thickness, weight uniformity, folding endurance, drug content, surface pH, swelling index.
- To Conduct *In vitro* dissolution studies, *Ex vivo* permeation studies, *In vitro* residence time and stability studies.

PLAN OF WORK....

4. PLAN OF WORK

- **LITERATURE SURVEY**
- **SELECTION OF DRUG, POLYMERS AND EXCIPIENTS**
- **PROCUREMENT OF DRUG, POLYMERS AND EXCIPIENTS**
- **EXPERIMENTAL WORK**
  - **Pre-formulation Study**
    - ✓ **Identification of Drug**
      - **Organoleptic properties of drug**
      - **Melting point**
      - **Solubility profile**
      - **UV-Spectroscopy (λ_{max})**
      - **Quantification of drug**
      - **FTIR Spectroscopy**
      - **DSC thermogram**
  - **Formulation of Mucoadhesive buccal patches**
  - **Characterization of buccal patches**
    - **Weight variation**
    - **Thickness uniformity**
    - **Folding endurance**
    - **Surface PH**
    - **Estimation of drug content**
    - **Fourier transformer infrared spectroscopy (FTIR)**

- ***In-vitro* residence time**
- ***In-vitro* drug release study**
- ***Ex-vitro* permeation study**
- **Swelling percentage study**
- **Kinetics of *in-vitro* drug release**
- **Stability study**

- **RESULTS AND DISCUSSION**
- **SUMMARY AND CONCLUSION**
- **FUTURE PROSPECTS**
- **BIBLIOGRAPHY**

MATERIALS AND EQUIPMENTS.....

5. MATERIALS AND EQUIPMENTS

5.1MATERIALS USED

Table 5.1: List of Polymers and Excipients with source

S.No.	Ingredients	Supplier
1	Tramadol hydrochloride	APEX pharmaceutical limited, Chennai.
2	Sodium alginate	Dr. Reddys pharmaceuticals limited, Mumbai.
3	Sodium carboxy methyl cellulose	SD fine-chem limited, Mumbai.
4	HPMC	Griffon laboratories Pvt. Ltd., Mumbai.
5	PVA	Hi-media laboratories, Mumbai.
6	Carbopol 934	SD fine-chem. limited, Mumbai.
7	Potassium dihydrogen orthophosphate	Fischer scientific chemicals, Mumbai.
8	Propylene glycol	Fischer scientific chemicals, Mumbai.
9	Sodium hydroxide	Fischer scientific chemicals, Mumbai.

5.2EQUIPMENTS USED :

Table 5.2: List of Equipments with model/make

S.No	Equipments	Model/ Make
1	Electronic balance	Shimadzu BL-220H.
2	Sonicator	2200MH, Soltech srl, Soluzioni Tecnologirhe, Milano, Italy.
3	Magnetic stirrer	1-MLH, remi equipments limited, vasai.
4	Digital pH meter	Elico scientifics-L1610, Mumbai.
5	UV spectrophotometer	Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer.
6	FTIR spectrophotometer	Shimadzu S4008.
7	Differential scanning calorimeter	Shimadzu DSC 60 with DTA, Japan.
8	Screw Gauge	J S export Ambala cantt.133006
9	Disintegration apparatus	Inco Instruments, Mumbai
11	Hot air oven	Sheetal Scientific Industries, Bombay
12	Incubator	Malveran instruments, Malvern, UK.
13	USP dissolution apparatus	Labtech.
14	Franz diffusion cell	Fabricated as per specifications .

EXPERIMENTAL WORK .....

6. EXPERIMENTAL WORK

6.1. PREFORMULATION STUDY

Before formulating a product, the physical and chemical properties of a drug substance have undergone some preformulation testing. It is the first step in rational development of dosage form.

6.1.1. Identification of drug

a) Identification by FTIR spectroscopy *(Skoog D.A., et al., 1996; IP, 2007)*

Tramadol hydrochloride discs were prepared by pressing the Tramadol hydrochloride with potassium bromide and the spectra in between 4000 to 500 cm^{-1} was obtained under the operational conditions. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum represented in Table 9.1 and shown in Figure 9.1.

b) Identification by melting point *(Moffat. et al., 2004)*

Melting point of the drug was determined by capillary tube method.

6.1.2. Physicochemical parameters

a) Organoleptic properties *(Lachman L.,et al.,1991)*

The color, odor and taste of the drug were recorded using descriptive terminology.

b) Solubility study *(Moffat. et al., 2004)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a

therapeutic response. The solubility of drug was recorded by using various descriptive terminologies. The solubility profile was represented in Table 9.2.

6.1.3. Analytical methods

a) Determination of λ max *(USP, 2009)*

The absorption maximum of the standard solution was scanned between 200-400 nm regions on UV-Visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

6.1.3.1. Development of standard curve of Tramadol hydrochloride:

(IP, 2007;USP,2009)

Preparation of Phosphate buffer (pH 6.8)

Phosphate buffer (pH 6.8) was prepared according to I.P. 2007. Placed 50 ml of 0.2 M potassium dihydrogen phosphate in a 200 ml volumetric flask and 22.4 ml of 0.2M sodium hydroxide was added and volume was made upto required quantity with water.

Preparation of 0.2M Potassium dihydrogen phosphate

Dissolved 27.218 gm of potassium dihydrogen phosphate in water and made up to 1000 ml.

Preparation of stock solution of with Tramadol hydrochloride pH 6.8

Accurately weighed 50 mg of Tramadol HCl, was dissolved in little quantity of pH 6.8 and volume was adjusted to 50 ml with the same to prepared standard solution having concentration of 1000 µg/ml. From that 1ml is pippeted out and makes upto 10ml to obtaine a concentration of 100 µg/ml.

Procedure

From the stock solution, aliquots of 0.5, 1, 1.5, 2 and 2.5 ml were transferred into 100 ml volumetric flasks and final volume was made upto 10 ml with pH 6.8. Absorbance values of these solutions were measured against blank (pH 6.8) at 271.5 nm using UV-Visible spectrophotometer.

Preparation of Phosphate buffer (pH 7.4)

Phosphate buffer (pH 7.4) was prepared according to I.P. 2007. Placed 31.2 ml of 0.2 M potassium dihydrogen phosphate in a 200 ml volumetric flask and 22.4 ml of 0.2M sodium hydroxide was added and volume was made upto required quantity with water.

Preparation of 0.2M Potassium dihydrogen phosphate

Dissolved 27.218 gm of potassium dihydrogen phosphate in water and made up to 1000 ml.

Preparation of stock solution of with Tramadol hydrochloride pH 7.4

Accurately weighed 50 mg of Tramadol HCl, was dissolved in little quantity of pH 7.4 and volume was adjusted to 50 ml with the same to prepared standard solution having concentration of 1000 µg/ml. From that 1ml is pippeted out and makes up to 10ml to obtaine a concentration of 100 µg/ml.

Procedure

From the stock solution, aliquots of 0.5, 1, 1.5, 2 and 2.5 ml were transferred into100 ml volumetric flasks and final volume was made up to 10 ml with pH 7.4. Absorbance values of these solutions were measured against blank (pH 7.4) at 271.5 nm using UV-Visible spectrophotometer.

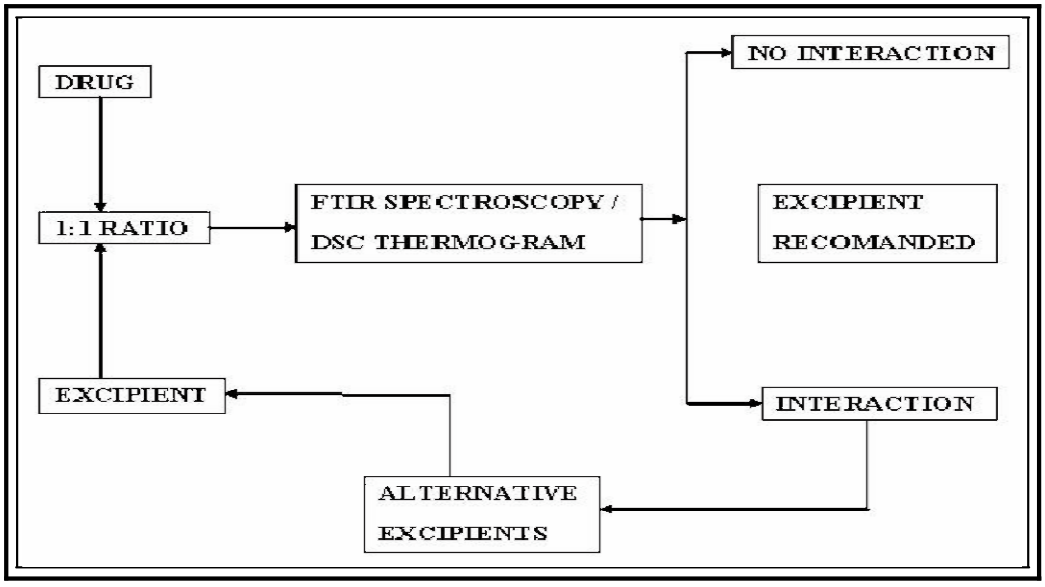
6.1.3.2. B) Determination of Percentage purity of Drug *(USP, 2009)*

Accurately weighed 50 mg of Tramadol HCl was dissolved in little quantity of distilled water to get the concentration of 1mg/ml. The solution was pipetted out of about 0.5 ml to 3 ml and volume was made up with distilled water. From the above stock solution, the concentration and absorbance was observed. The absorbance was measured at 271.5 nm against the blank using by UV-Visible spectrophotometer. The percentage purity of drug was calculated by using calibration curve method (least square method).

6.1.4. DRUG EXCIPIENT INTERACTION STUDIES

6.1.4. a) Determination of drug-polymer compatibility ***(****Aulton M.E.,et al.,2002)*

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients.



Schematic representation of compatibility studies

6.1.4. b) Fourier transform Infra-Red (FTIR) spectroscopy *(IP, 2007)*

FTIR study was carried out to check compatibility of drug with polymers. Fourier transform Infrared Spectrophotometer was determined by using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of Tramadol HCl and potassium bromide was run followed by Tramadol HCl with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum was represented.

6.1.4. c) Differential scanning calorimetry (DSC) **(***AultonM.E., et al.,2002)*

Any possible drug polymer interaction can be studied by thermal analysis. The DSC study was performed on pure Tramadol HCl, Tramadol HCl + HPMC, Tramadol HCl + carbopol-934 , Tramadol HCl + sodium alginate and Tramadol HCl + NaCMC. The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30ml/min.

FORMULATION OF MUCOADHESIVE BUCCAL PATCHES....

7. FORMULATION OF MUCOADHESIVE BUCCAL PATCHES

Table 7.1: Composition of mucoadhesive buccal patches of Tramadol hydrochloride

FORMU-LATIONS	TRAMADOL HCl (mg)	SA (mg)	HPMC (mg)	CP 934 (mg)	NaCMC (mg)	PROPYLENE GLYCOL %	DISTILLED WATER (ml)
F1	50	900	100	-	-	10	40
F2	50	800	200	-	-	10	40
F3	50	700	300	-	-	10	40
F4	50	900	-	100	-	10	40
F5	50	800	-	200	-	10	40
F6	50	700	200	100	-	10	40
F7	50	700	100	200	-	10	40
F8	50	700	200	-	100	10	40
F9	50	600	100	-	300	10	40

PREPARATION OF MUCOADHESIVE BUCCAL PATCHES BY SOLVENT CASTING METHOD: (*surya N. Ratha Adhikari .,et al.,2010)*

The Buccal Patches were preferably formulated using the solvent casting method. The Required quantity of polymer was added in small quantities and mixed well to dissolved in distilled water. Drug dissolved in the above solution in small quantities. Plasticizer added to the above solution and mixed well. Solution was then poured into petridishes and kept in hot air oven for drying at 40˚ C. After drying patches were removed with the help of sharp blade and kept in desicator for 24 hrs then cut into pieces of the desired shape and size.

STEPS INVOLVED IN PREPARATION

- Backing membrane was casted by pouring 4% w/v aqueous solution of PVA on aluminum foil in 9 cm petridishes at 42°C and left for 10 h. Phosphate buffer saline, pH 6.8, was used as solvent in the casting method.
- A series of buccal patches composed of different ratios and combinations of polymers were prepared by solvent casting technique.
- Propylene glycol was incorporated as a plasticizer & penetration enhancer at a concentration of 10% w/w of dry weight of polymers.
- Fifty milligrams of Tramadol HCl was incorporated in mixtures containing different ratios and combinations of polymers and plasticizer. The matrices were prepared by pouring 40 ml of the homogeneous solutions on the PVA-aluminum foil backing membrane. Then, these buccal patches were dried at 42°C in an incubator. After 24 h, the dried patches were removed from the petri dishes and kept in desiccators until use.

EVALUATION OF BUCCAL PATCHES....

8. EVALUATION OF TRAMADOL HYDROCHLORIDE BUCCAL PATCHES

The Tramadol hydrochloride Buccal Patches were evaluated for the following properties:

8.1. Physical parameters

- Physical appearance and surface texture
- Weight Uniformity
- Thickness uniformity
- Folding Endurance
- Swelling Index.
- Surface pH

8.2. Mechanical parameters

- *In vitro* residence time
- *In vitro* drug release
- content uniformity
- *Ex vivo* permeation studies

8.1. Physical parameters: *(Padmaja Chimmiri .,et al.,2012)*

a) Physical appearance and surface texture of patch:

This parameter was checked simply with visual inspection of patches and evaluation of texture by feel or touch.

b) Weight Uniformity of patches:

Three patches of the size 29 mm diameters were weighed individually using digital balance and the average weights were calculated.

c) Thickness of patches:

Thickness of the patches was measured using screw gauge with a least count of 0.01mm at different spots of the patches. The thickness was measured at three different spots of the patches and average was taken.

d) Folding Endurance of patches:

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patches (approximately 2x2 cm) at the same place till it broke. The number of times patches could be folded at the same place, without breaking gives the value of folding endurance.

e) Swelling Index of patches:

The swelling Index of the patches determined by immersing pre weighed patch of size 29mm in 50 ml water. The strip were taken out carefully at 5 and 10 min. intervals, blotted with filter paper and weighed accurately.

$$\textbf{\% Swelling Index} = \frac{\textbf{Wet Weight – Dry Weight}}{\textbf{Wet Weight}} \times 100$$

f)Surface pH of patches:

Surface pH was determined by the patches were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patches and allowing to equilibrate for 1 min.

8.2. Mechanical parameters

8.2.1*In vitro* residence time

The in *vitro* residence time was determined employing a modified USP disintegration apparatus. The disintegration medium was composed of 800 ml isotonic phosphate buffer of pH 6.8 (IPB) maintained at 37± 0.5^{0}C. A piece of porcine buccal tissue, 3 cm length was used for this study. The tissue was attached to a rectangular glass piece using cyanoacrylate adhesive from non-mucosal surface. The mucoadhesive patch was hydrated from one surface using pH 6.8 IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was observed and recorded (n=3).

8.2.2 *In vitro* release study ***(****Raghvendra Rao NG., et al.,2011.)*

The *in vitro* drug release studies were performed by using USP dissolution test apparatus (paddle method) .A film of 29mm diameter size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.8). This slide was kept at an angle of 45º in a 1000 ml beaker containing 250 ml of phosphate

buffer pH 6.8 solutions. The dissolution medium was maintained at a temperature of 37 ± 0.5º C and stirred at 50 rpm. At predetermined time intervals samples were withdrawn and replaced with fresh dissolution medium. The samples were filtered through 0.45µm Whatman filter paper and made appropriate dilutions with phosphate buffer pH (6.8). Absorbance was measured using UV- VISIBLE spectrophotometer. Drug release and the cumulative percentage of drug released were determined

Table 8.1: Parameters were used for the dissolution study

Apparatus	USP Dissolution apparatus (Type I)
Dissolution medium	Phosphate buffer (pH 6.8)
Temperature	37 ± 0.5 °C
Volume	250 ml
Speed	50 rpm
Sample withdrawn	5 ml
Running Time	7hrs

8.2.3 Content Uniformity ***(Padmaja Chimmiri .,et al.,2012)***

Content uniformity was determined by dissolving one patch of 29mm diameter contain 5 mg of Tramadol Hydrochloride in 10 ml of phosphate buffer solution (pH6.8). And the contents were stirred with the help of magnetic stirrer to dissolve the film. The contents of solution were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank

solution at 271 nm using UV spectrophotometer. The experiments were carried out in triplicate for each formulation and average value was calculated.

8.2.4 *Ex vivo permeation* studies

Sheep buccal mucosa was used as a barrier membrane. The buccal mucosa of freshly sacrificed sheep was procured from the local slaughter house. The buccal mucosa washed in isotonic phosphate buffer of pH 6.8 and used immediately. The permeability across the sheep buccal membrane was determined in order to evaluate diffusion studies by using Franz diffusion cell.

The buccal mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 25 ml of isotonic phosphate buffer of pH6.8 which was maintained at 37 ± 0.2º C and stirred with a magnetic bead at 50 rpm. At regular intervals of time samples were withdrawn and diluted appropriately and absorbance was analyzed using an UV-VIS spectrophotometer at 271 nm.

8.2.5 Kinetics of *In-vitro* drug release

In-vitro drug released data was subjected to *in- vitro* kinetic models such as zero order, first order, Higuchi and Korsemeyer- Peppas.

Zero order:

$$C = K_0 t$$

Where K_0 - is the zero-order rate constant expressed in units of concentration/time

t -is the time in hrs.

First order:

$$Log\ C = LogC_0 - Kt / 2.303$$

Where C_0 - is the initial concentration of drug,

K - is the first order constant

t - is the time in hrs.

Higuchi:

$$Qt = Kt^{1/2}$$

Where Q_t - is the amount of the release drug in time t,

K- is the kinetic constant and t- is time in hrs

KorsmeyerPeppas:

$$Mt/ M\infty = Kt\ n$$

Where M_t - represents amount of the released drug at time t,

M_∞- is the overall amount of the drug (whole dose) released after 12 hrs

K- is the diffusional characteristic of drug/ polymer system constant

n- is a diffusional exponent that characterizes the mechanism of release of drug.

Table 8.2: Diffusion exponent and solute release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
< 0.5	Quasi-Fickian diffusion
0.5	Fickian diffusion
0.5 < n < 1.0	Anomalous (non-Fickian) diffusion
1.0	Case-II transport
> 1.0	Super case-II transport

8.2.6 STABILITY STUDIES *(Manavalan R. and Ramasamy S., 2004)*

In any rational drug design or evaluation of dosage forms, the stability of the active component was a major criterion in determining their acceptance or rejection.

Objective of the study

The purpose of stability testing was to provide the evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions

Long-Term Testing:

Room temperature; 25° C ±2° C at 60% RH ±5% for12 months

Accelerated Testing:

Accelerated temperature ;40°±2° C at 75%RH ±5% for 6 Months In present study the optimized formulation F9 was exposured up to 3 months stability studies at accelerated condition (40° C ±2° C at 75% RH ±5%RH) to find out the effect of aging on drug content and *In-vitro* drug release.

Procedure

The formulation (F7) was stored at accelerated condition in aluminum foils for 3 months. The samples were withdrawn after end of 1st month, 2nd month and 3rd month. The samples were analyzed for its drug content and i*n vitro* drug release.

RESULTS AND DISCUSSION

9. RESULTS AND DISCUSSION

9.1. PREFORMULATION PARAMETERS

9.1.1. Identification of drug by FTIR spectroscopy

The FTIR spectrum of Tramadol hydrochloride was shown in Figure 9.1 and the interpretations of IR frequencies were represented in Table 9.1.

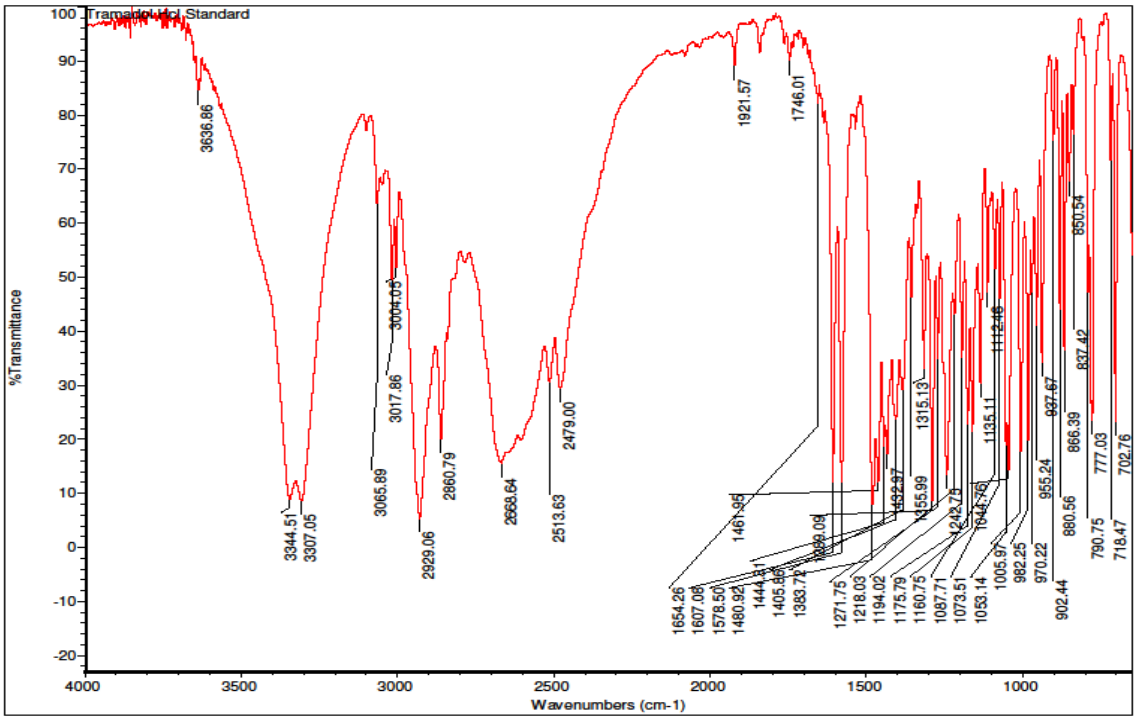


Figure 9.1: FTIR spectrum of Tramadol hydrochloride

Interpretation of FTIR Spectrum

Major functional groups present in Tramadol HCl show characteristic peaks in FTIR spectrum. The major peaks are identical to functional group of Tramadol HCl Hence, the sample was confirmed as Tramadol HCl.

Table 9.1: Characteristic frequencies in FTIR spectrum of Tramadol HCl

Inference	Wave no.(cm^{-1})
N-H stretching,O-H stretching	3636-3307
C-H stretching(in-plane)	3065-2860
C=C stretching	2668-1578
C-H bending	1461-1383
C-O Stretching	1289-1053
C-N Stretching	1194-1289
C-H bending(out-plane)	837-982

b) Melting point

Melting point values of Tramadol HCl sample was found to be in range of 180° C to 184° C .The reported melting point for Tramadol HCl was 181±1.15^0 C. Hence, experimental values were same as official values.

9.1.2. Physicochemical parameters of drug

Organoleptic properties:

Physical state: Fine powder

Colour : A white fine powder

Odour : Characteristic

Taste : Bitter to alkaline

Solubility study

Table: 9.2 Solubility of Tramadol HCl in various solvents

Name of solvent	Standard Parts of solvent required for part of solute	Solubility
Distilled water	From 1 to 10	Freely Soluble
Methanol	From 10 to 30	Soluble
Isopropyl alcohol	From 100 to 1000	Slightly soluble
pH 6.8	From 10 to 30	Soluble
pH 7.4	From 10 to 30	Soluble
Glacial acetic acid	More than 10000	Partially insoluble
Acetone	More than 10000	Partially insoluble

9.2Analytical methods

DETERMINATION OF λ MAX OF TRAMADOL HCl BY USING DISTILLED WATER BY UV SPECTROPHOTOMETRY:

The absorption maximum for Tramadol hydrochloride was found at 271.5nm

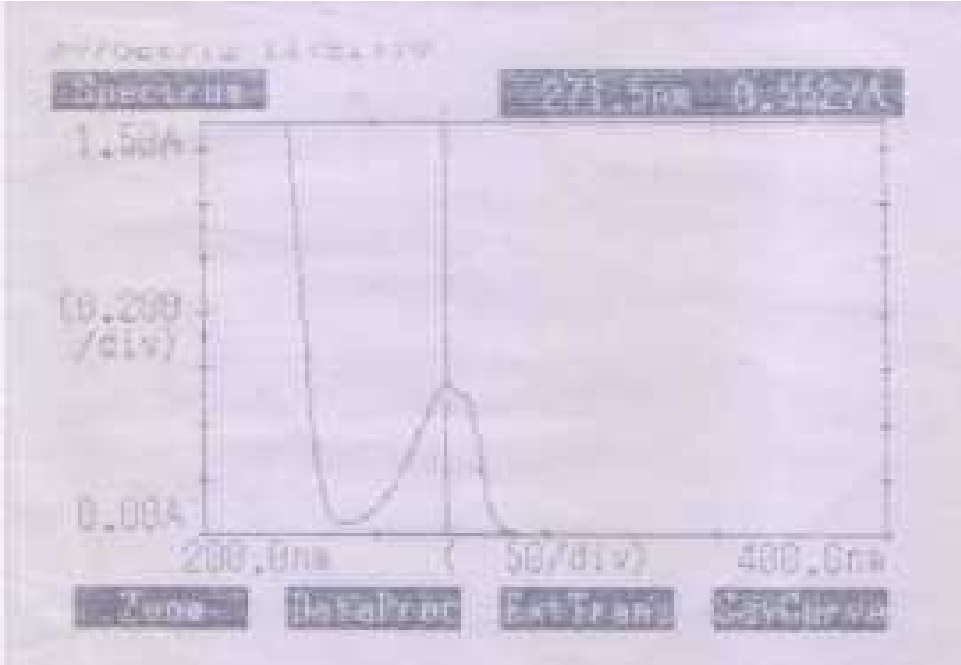


Figure 9.2: λ max observed for Tramadol HCl in distilled water.

Preparation of standard graph of Tramadol hydrochloride

UV absorption spectrum of Tramadol hydrochloride in distilled water showed λ max at 271.5 nm was shown in figure 9.2 Absorbance obtained for various concentrations of Tramadol hydrochloride in distilled water were represented in Table 9.3. The graph of absorbance vs. concentration for Tramadol hydrochloride was found to be linear in the concentration range of 5–25 μg/ml. The drug obeys Beer- Lambert's law in the range of 5–25 μg /ml was shown in figure 9.3.

Table 9.3: Data of concentration and absorbance for Tramadol HCl in distilled water

S.No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.180
3	10	0.361
4	15	0.552
5	20	0.772
6	25	0.940

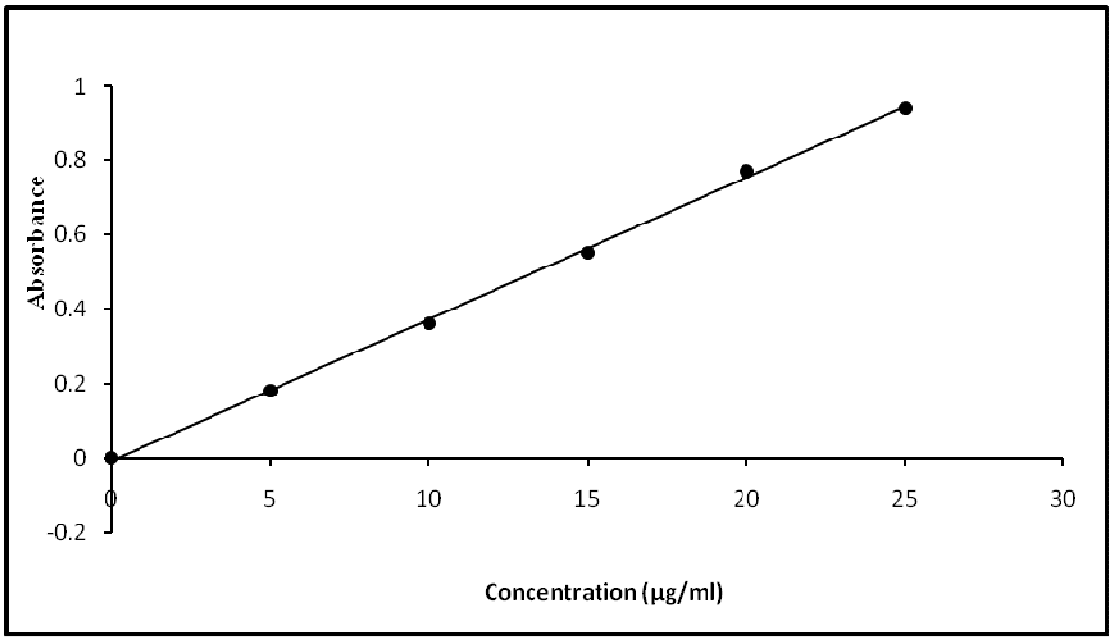


Figure 9.3: Standard curve for Tramadol hydrochloride in distilled water

Table 9.4 Data for calibration curve parameters for distilled water

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9995
2	Slope	0.026
3	Intercept	0.2420

DETERMINATION OF λ MAX OF TRAMADOL HCl BY USING pH6.8 BY UV SPECTROPHOTOMETRY:

The absorption maximum for Tramadol hydrochloride was found at 271.5nm

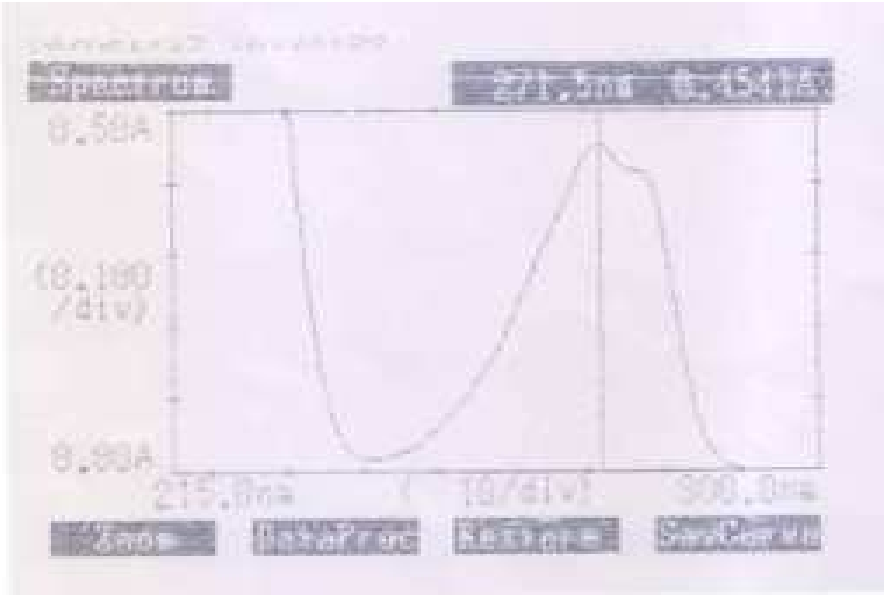


Figure 9.4: λ max observed for Tramadol HCl in pH 6.8(phosphate buffer).

Preparation of standard graph of Tramadol hydrochloride

UV absorption spectrum of Tramadol hydrochloride in pH 6.8(phosphate buffer) showed λ max at 271.5 nm was shown in figure 9.4. Absorbance obtained for various concentrations of Tramadol hydrochloride in pH 6.8 were represented in Table 9.5. The graph of absorbance vs. concentration for Tramadol hydrochloride was found to be linear in the concentration range of 5–25 μg/ml. The drug obeys Beer- Lambert's law in the range of 5–25 μ/ml was shown in figure 9.5.

Table 9.5:Data of concentration and absorbance for Tramadol HCl in pH6.8

S.No.	Concentration (μg/ml)	Absorbance
1	0	0.000
2	5	0.150
3	10	0.303
4	15	0.454
5	20	0.602
6	25	0.754

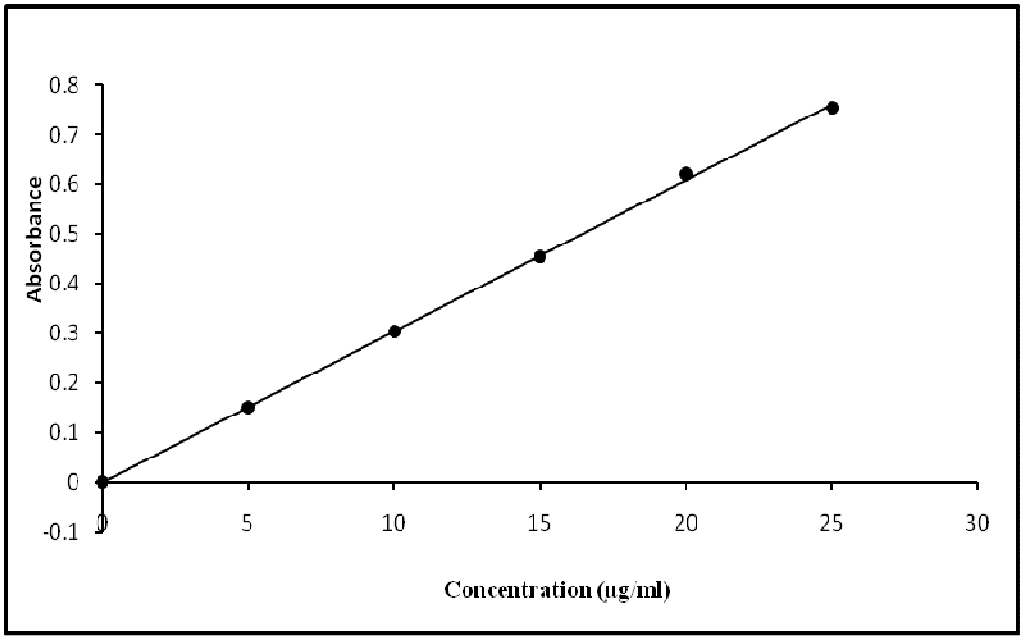


Figure 9.5: Standard curve for Tramadol hydrochloride in pH 6.8

Table 9.6 Data for calibration curve parameters in pH 6.8.

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9998
2	Slope	0.032
3	Intercept	0.0261

DETERMINATION OF λ MAX OF TRAMADOL HCl BY USING pH 7.4 BY UV SPECTROPHOTOMETRY :

The absorption maximum for Tramadol hydrochloride was found at 271.5nm

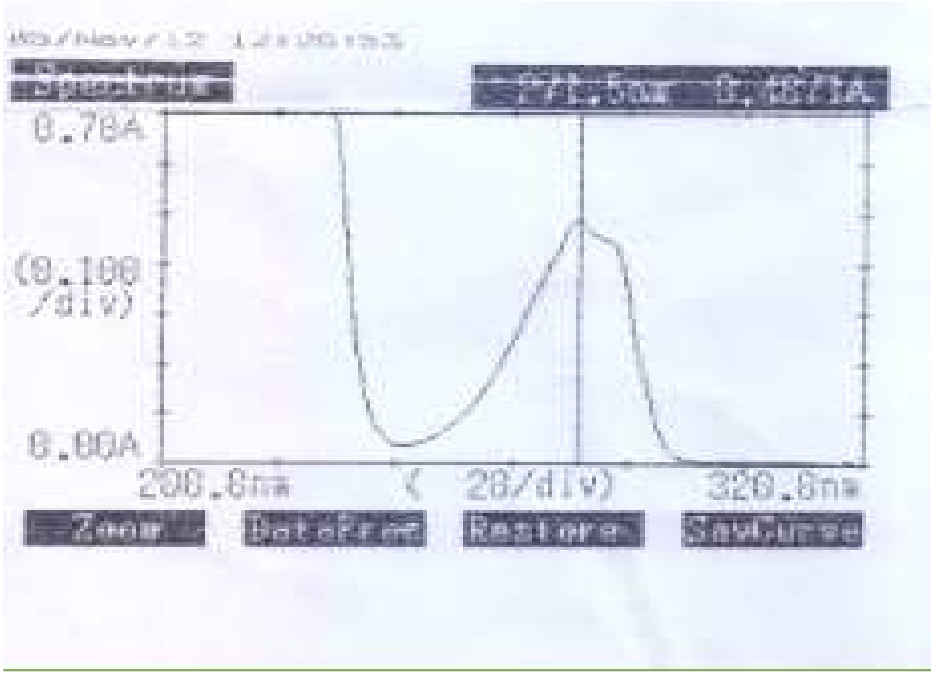


Figure 9.6: λ max observed for Tramadol HCl in pH 7.4(phosphate buffer).

Preparation of standard graph of Tramadol hydrochloride

UV absorption spectrum of Tramadol hydrochloride in pH 7.4(phosphate buffer) showed λ max at 271.5 nm was shown in figure 9.6. Absorbance obtained for various concentrations of Tramadol hydrochloride in pH 7.4 were represented in Table9.7. The graph of absorbance vs. concentration for Tramadol hydrochloride was found to be linear in the concentration range of 5–25 µg/ml. The drug obeys Beer- Lambert's law in the range of 5–25 µg/ml was shown in figure 9.7.

Table 9.7: Data of concentration and absorbance for Tramadol HCl in pH 7.4

S.No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.162
3	10	0.324
4	15	0.487
5	20	0.672
6	25	0.811

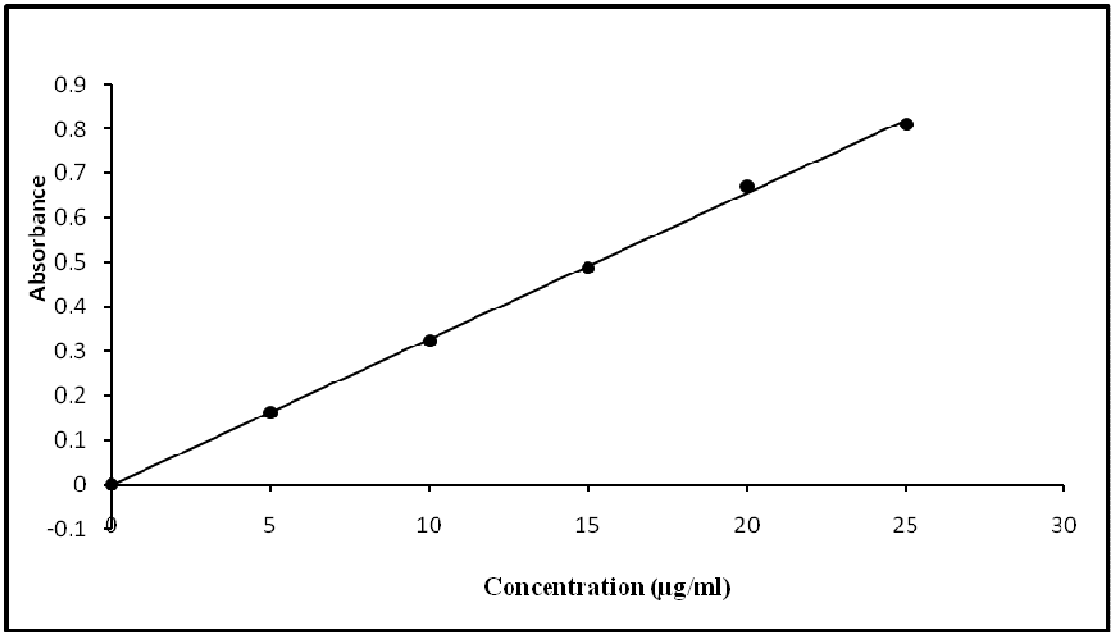


Figure 9.7: Standard curve for Tramadol hydrochloride in pH 7.4

Table 9.8 Data for calibration curve parameters in pH7.4

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9996
2	Slope	0.0613
3	Intercept	0.0477

Percentage purity of drug

The percentage purity of drug was calculated by using calibration graph method (least square method).

Table: 9.9 Data of percentage purity of drug

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	99.87	100.11±0.240
2	100.12	
3	100.35	

*All values are expressed as mean± S.D., n=3

The percentage purity for Tramadol Hcl in BP 2009 is not less than 99.0 % and not more than 101.0 % of the stated amount of Tramadol HCl.

Determination of compatibility for drug with polymer by FTIR spectroscopy

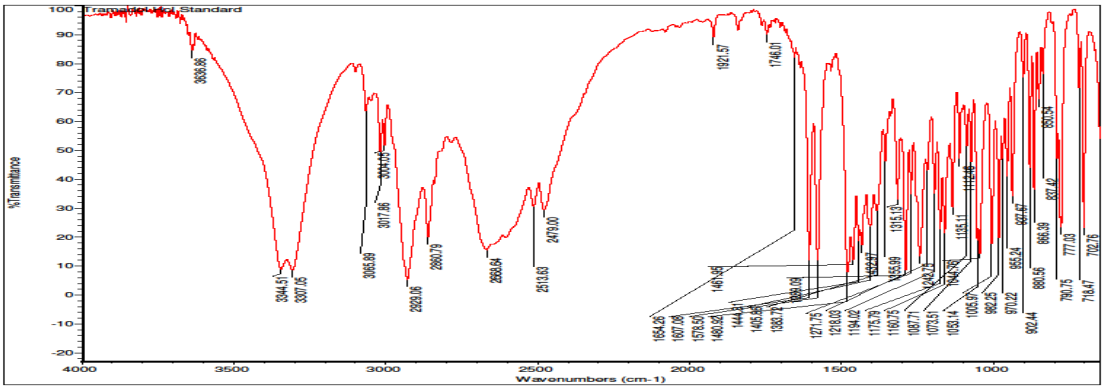


Figure 9.8 FTIR spectra of Tramadol HCl

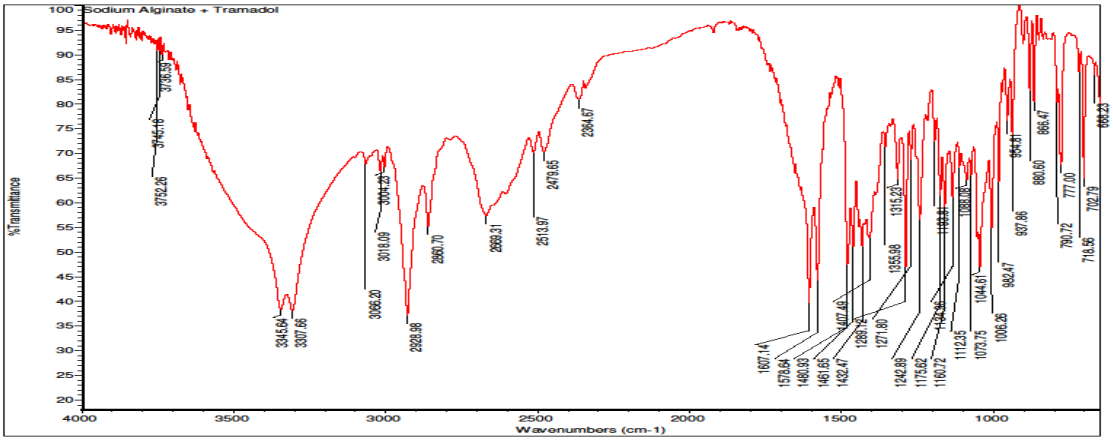


Figure 9.9 FTIR spectra of Tramadol HCl with sodium alginate

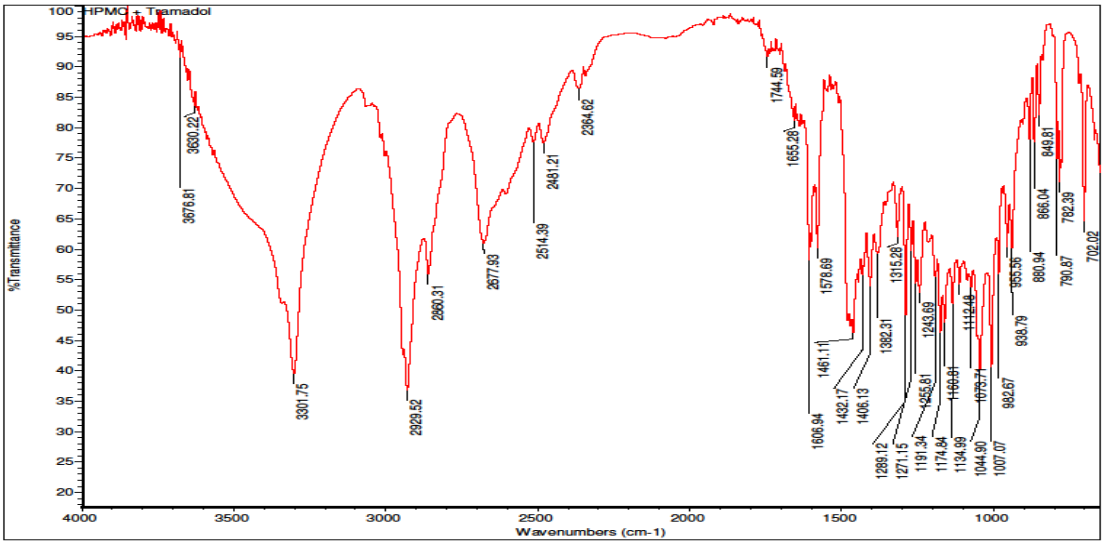


Figure 9.10 FTIR spectra of Tramadol HCl with HPMC

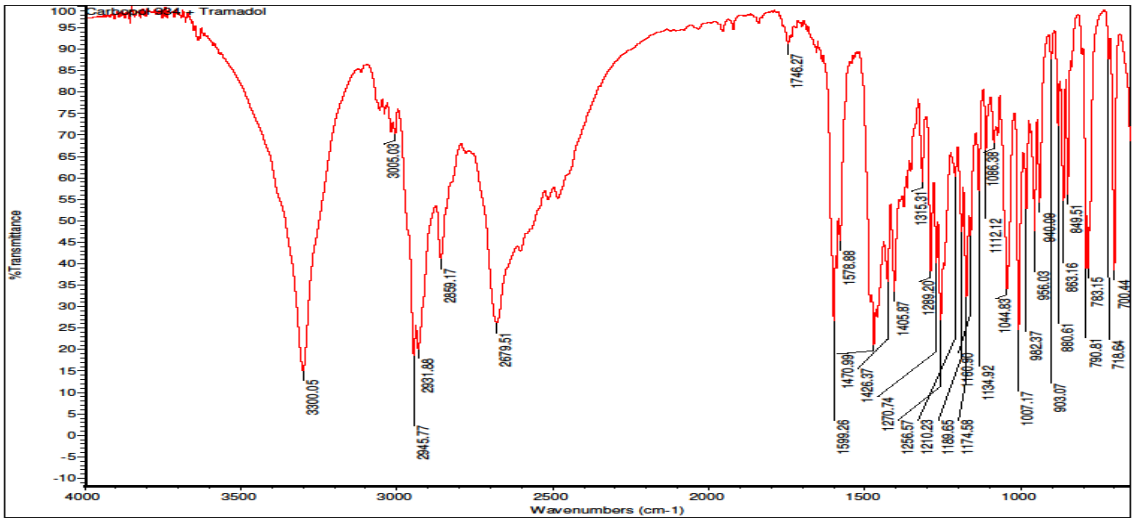


Figure 9.11 FTIR spectra of Tramadol HCl with carbopol 934

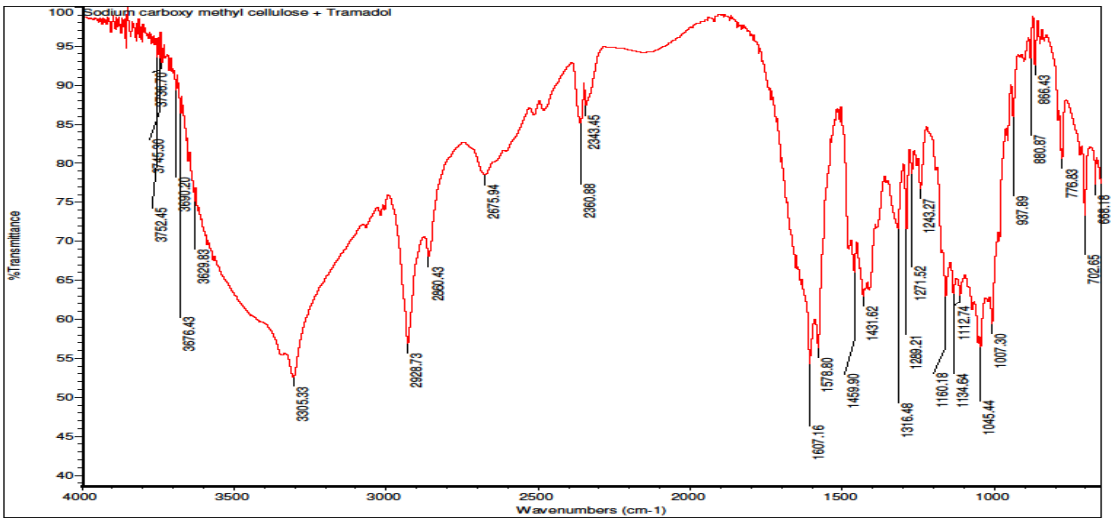


Figure 9.12 FTIR spectra of Tramadol HCl with NaCMC

Table 9.10 The major peak observed in FTIR spectrum of Tramadol HCl and Tramadol HCl with different polymers used in formulations.

Wave No. (cm^{-1})	Functional group	Peak observed (Yes/No)				
		Tramadol HCl	Tramadol HCl + Sodiumalginate	Tramadol HCl + HPMC	Tramadol HCl + carbopol 934	Tramadol HCl + NaCMC
3636-3307	N-H,O-H Stretching	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
3065-2860	C-H Stretching	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
2668-1578	C=C stretching	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
1461-1383	C-H bending (in-plane)	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
1289-1053	C-O Stretching	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
1194-1289	C-N Stretching	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
837-982	C-H bending (out-plane)	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

The major peaks of Tramadol hydrochloride spectrum were compared to Tramadol hydrochloride with polymers spectrum. There was no interaction between Tramadol Hydrochloride and polymers .The peaks were represented in table 9.10 and spectrums where shown in figure 9.8 to 9.12.

DSC thermal analysis:

The interactions between Tramadol hydrochloride and polymers were determined by DSC studies and results were represented in Table 9.11 and Thermogram curves where shown in Figure 9.13 to 9.17.

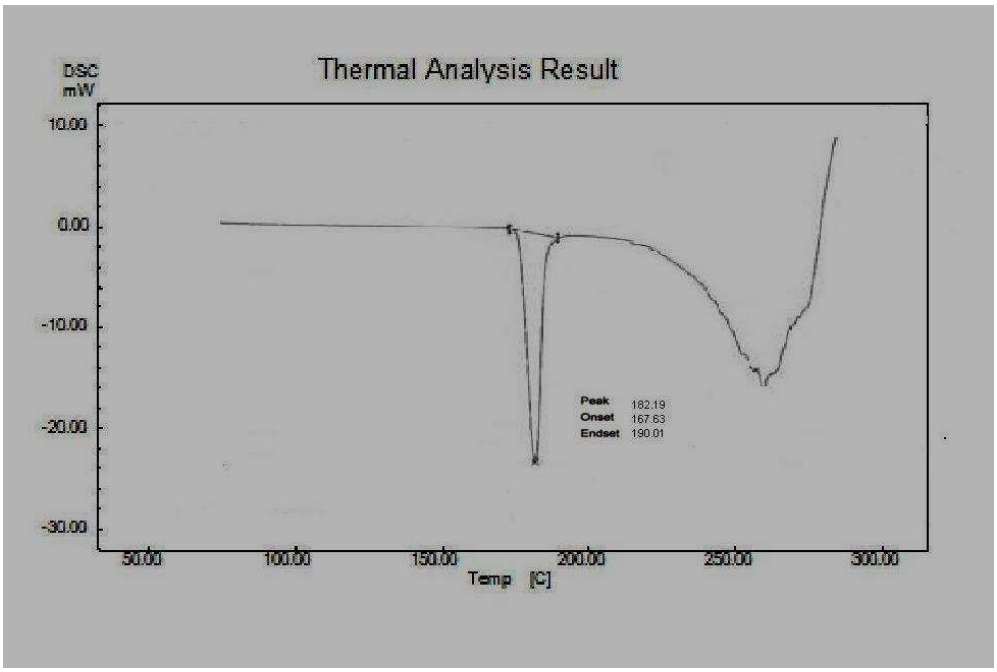


Figure 9.13: DSC thermogram for Tramadol hydrochloride

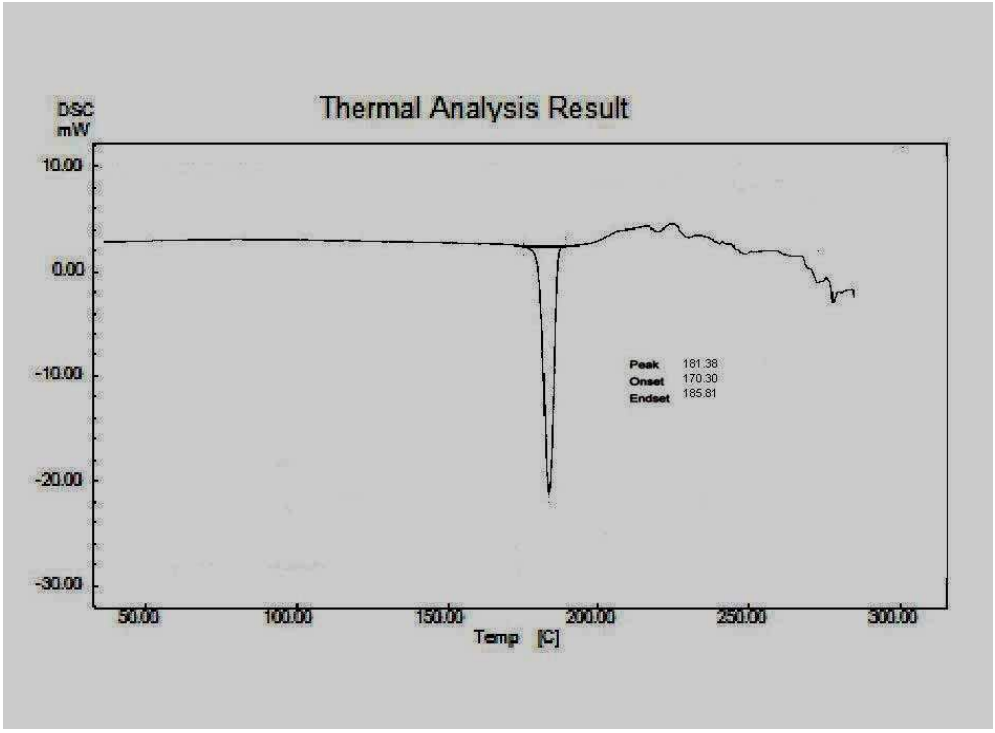


Figure 9.14: DSC thermogram for Tramadol hydrochloride with Sodium alginate

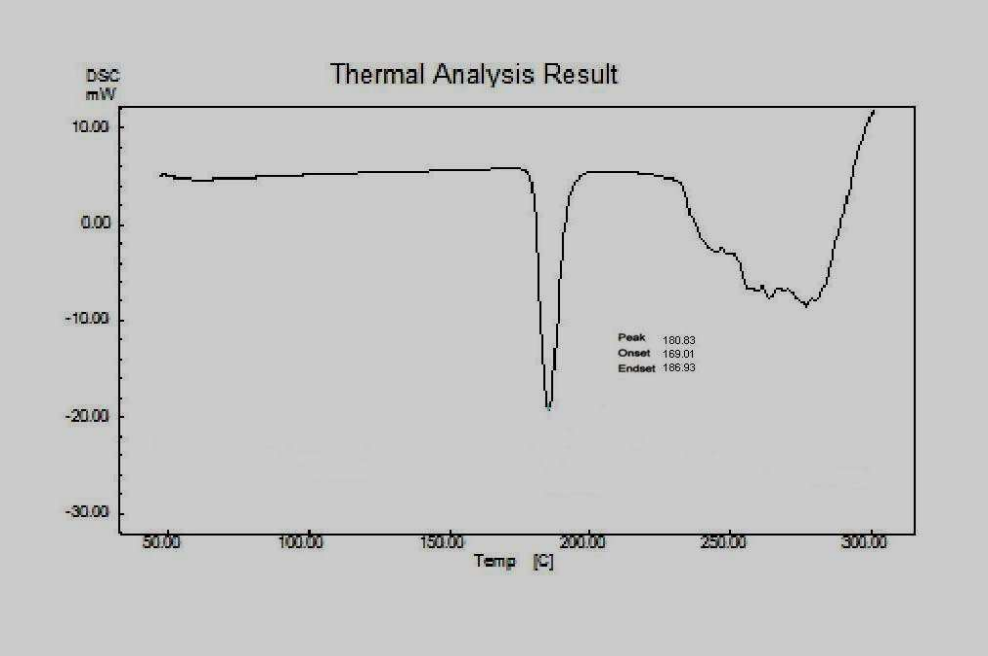


Figure 9.15: DSC thermogram for Tramadol hydrochloride with carbopol 934

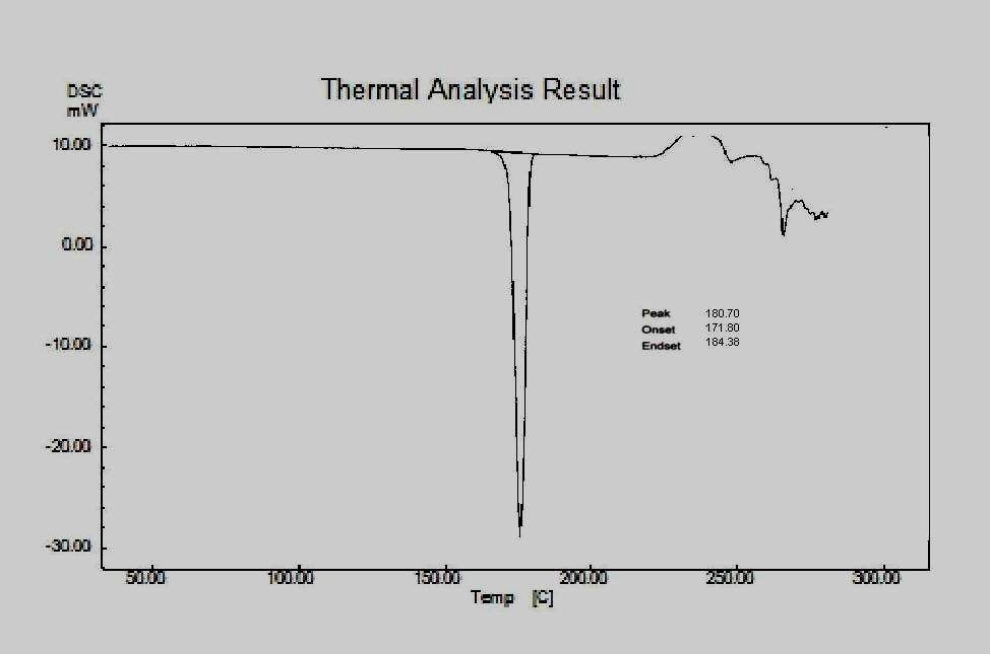


Figure 9.16: DSC thermogram for Tramadol hydrochloride with HPMC

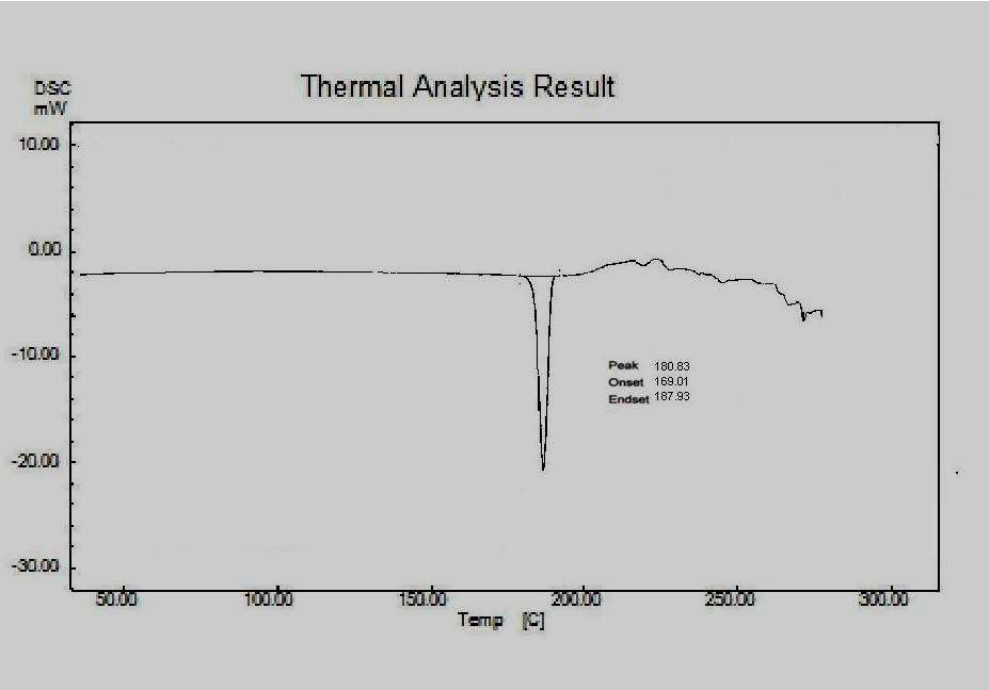


Figure 9.17: DSC thermogram for Tramadol hydrochloride with NaCMC

Table 9.11: Various DSC thermogram parameter

S. No.	DSC Graphs	Peak (ºC)	Onset temperature (ºC)	Endset temperature (ºC)
1	Tramadol Hcl	182.19	167.63	190.01
2	Tramadol Hcl + sodium alginate	181.38	170.30	185.81
3	Tramadol Hcl + carbopol 934	180.83	169.01	186.93
4	Tramadol Hcl + HPMC	180.70	171.80	184.38
5	Tramadol Hcl + NaCMC	180.83	169.01	187.93

9.3 EVALUATION OF TRAMADOL HYDROCHLORIDE LOADED MUCOADHESIVE BUCCAL PATCHES

Physical appearance and surface texture of patches:

These parameters were checked simply with visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surface and they are elegant in appearance.

Weight uniformity of patches:

The weight of the patches was determined using digital balance and the average weight of all patches was given in Table 9.12.

The drug loaded patches (29 mm) were tested for uniformity of weight. The patches were found uniform in weight. The average weight of formulation F1 , F2 and F3 composed of polymers such as sodium alginate and HPMC in various ratios were weighed about 34.66 ± 1.15 , 37.66 ±0.57 and 43.33 ±1.15 mg respectively. Formulation F4 and F5 composed of polymers such as sodium alginate and carbapol 934 in various ratios were weighed about 33.33 ±1.15 and 28.66 ±1.15 mg respectively. Formulation F6 and F7 composed of polymers such as sodium alginate , HPMC and carbapol 934 in various ratios were weighed about 25.00 ±1.73 and 27.66 ±1.52 mg respectively**.** Formulation F8 and F9 composed of polymers such as sodium alginate, HPMC and NaCMC in various ratios were weighed about 45.66 ±1.52 and 47.66±0.57 mg respectively**.**

In all the cases the calculated standard deviation values were very low which they suggest that the prepared patches were uniform in weight.

Thickness of patches:

The thickness of the patches was measured using screw gauge and the average thickness of all patches was given in Table 9.12.

The drug loaded patches (29 mm) were tested for thickness. . The average thickness of formulation F1, F2 and F3 composed of polymers such as sodium alginate and HPMC in various ratios were about 0.55±0.05**,** 0.56±0.05 and 0.52±0.05 mm respectively. The average thickness of formulation F4 and F5 composed of polymers such as sodium alginate and carbapol 934 in various ratios were about 0.58±0.01 and 0.53 ±0.05 mm respectively. The average thickness of formulation F6 and F7 composed of polymers such as sodium alginate, HPMC and carbapol 934 in various ratios were about 0.57±0.05 and 0.52±0.01 mm respectively**.** The average thickness of formulation F8 and F9 composed of polymers such as sodium alginate, HPMC and NaCMC in various ratios were about 0.54±0.05 and 0.58±0.05 mm respectively**.**

In all the cases the calculated standard deviation values were very low which they suggest that the prepared patches were uniform in thickness

Folding endurance of patches:

The folding endurance gives the idea of flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches was given in Table 9.12.

The drug loaded patches (29 mm) were tested for folding endurance. . The average folding endurance of formulation F1, F2 and F3 composed of polymers such as sodium alginate and HPMC in various ratios were about 263.33±3.51, 266.00±1.00 and 266.66±3.351 respectively. The average folding endurance of formulation F4 and F5 composed of polymers such as sodium alginate and carbapol 934 in various ratios were about 243.33±2.08 and 287.33±4.50 respectively. The average folding endurance of formulation F6 and F7 composed of polymers such as sodium alginate, HPMC and carbapol 934 in various ratios were about 249.66±2.08 and 293.33±2.64 respectively. The average folding endurance of formulation F8 and F9 composed of polymers such as sodium alginate, HPMC and NaCMC in various ratios were about 238±1.95 and 276.66±2.0 respectively.

Surface pH of patches:

Surface pH was determined by bring the patches in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patches and allowing equilibrate for 1 min and the average surface pH of all patches was given in Table 9.12.

The drug loaded patches (29 mm) were tested for Surface pH. . The average Surface pH of formulation F1 , F2 and F3 composed of polymers such as sodium alginate and HPMC in various ratios were about 6.33±0.57 , 6.16±0.05 and 5.76±0.05 respectively. The average Surface pH of formulation F4 and F5 composed of polymers such as sodium alginate and carbapol 934 in various ratios were about 6.46±0.17 and 6.43±0.35 respectively. The average Surface pH of

formulation F6 and F7 composed of polymers such as sodium alginate, HPMC and carbapol 934 in various ratios were about 5.8±0.37 and 6.4±0.26 respectively. The average Surface pH of formulation F8 and F9 composed of polymers such as sodium alginate, HPMC and NaCMC in various ratios were about 5.76±0.15 and 6.33±0.20 respectively.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymer, the surface pH of the buccal patches was determined to optimize both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close to buccal /salivary pH as possible, by the proper selection of the polymer for developing the buccal patches. The surface pH of all the patches was within the range of salivary pH. No significant difference was found in surface pH of prepared patches.

Table-9.12: Physical evaluation of mucoadhesive buccal patches of Tramadol HCl

Formulations	Average Weight (mg)	Average Thickness (mm)	Average Folding Endurance	Surface pH
F1	34.66 ± 1.15	0.55±0.05	263.33±3.51	6.33±0.05
F2	37.66 ±0.57	0.56±0.05	266 ±1.00	6.16 ±0.05
F3	43.33 ±1.15	0.52±0.05	266.66±3.51	5.76±0.11
F4	33.33 ±1.15	0.58±0.01	243 .33±2.08	6.46 ±0.05
F5	28.66 ±1.15	0.53 ±0.05	287.33±4.50	6.43±0.35
F6	25.000 ±1.73	0.57±0.05	249.66 ±2.08	5.8±0.37
F7	27.66 ±1.52	0.52±0.01	293.33±2.64	6.4±0.26
F8	45.66 ±1.52	0.54±0.05	238 ±1.95	5.76±0.15
F9	47.66±0.57	0.58±0.05	276.66±2.0	6.33±0.20

*All values are expressed as mean± S.D., n=3

Swelling index of patches:

The swelling index of the patches was determined by immersing preweighed patch of size 10 mm in 50 ml water. The patches were taken out from petridish care fully at 1,2,3,4,5,6 upto and 7 hr. intervals, blotted with filter paper and weighed accurately and the average swelling index of all patches was given in Table 9.13.

- The evaluated patches showed high swelling index values 0f about **25.01%** after 7hr in the case of formulation F7 due to the high swelling property of the polymer carbopol 934.

Table:9.13 :Data for swelling percentage studies

FORMULATIONS	SWELLING % WEIGHT INCREASES						
	1st hr	2nd hr	3rd hr	4th Hr	5th Hr	6th hr	7th Hr
F1	12.48	12.52	12.68	13.12	13.43	14.03	14.21
F2	11.82	11.92	11.92	11.98	12.04	12.58	13.02
F3	12.34	12.48	12.97	13.00	13.46	14.51	15.18
F4	16.12	16.41	16.48	16.80	16.81	16.95	17.01
F5	15.01	15.15	15.60	15.64	15.90	16.00	16.12
F6	17.3	17.48	17.80	17.90	18.15	18.30	18.41
F7	21.4	22.10	22.60	23.50	23.90	24.75	25.01
F8	14.82	14.90	15.00	15.45	15.80	15.85	15.91
F9	13.96	14.00	14.08	13.14	13.00	12.90	12.50

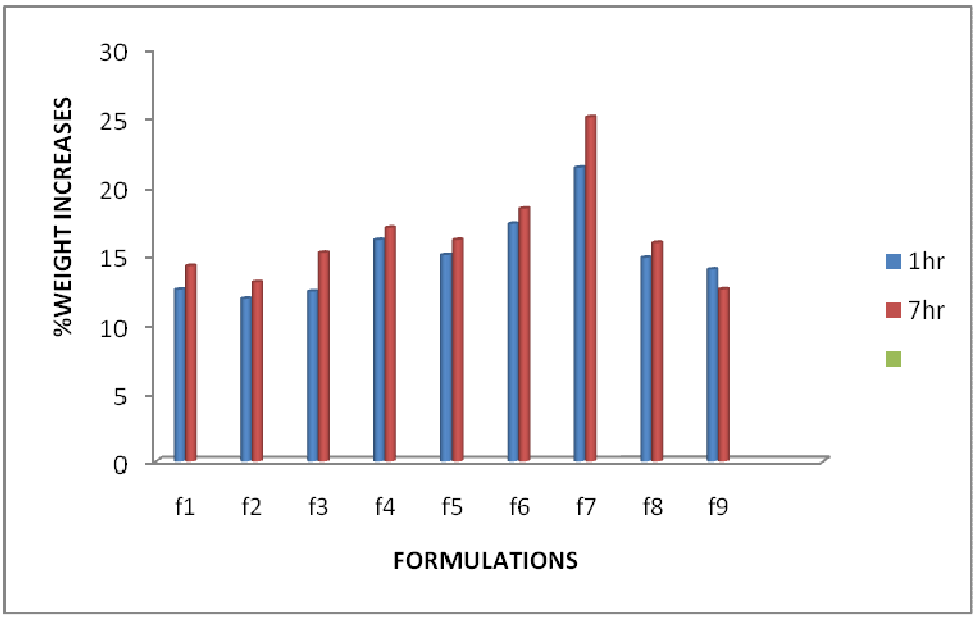


Figure 9.18 Comparative Swelling index of formulation F1 to F9

Drug content uniformity of patches:

Tramadol HCl buccal patches prepared with various polymers were subjected to the evaluation for uniform dispersion of drug throughout the patch. In each case three patches were used and the average drug content was calculated, the results were represented in Table-9.14. The drug was dispersed in the range of 90.14 ± 0.07 to 98.75 ± 0.80 %. Suggesting that drug was uniformly dispersed throughout all prepared patches.The standard deviation value calculated for such formulation is very less which suggest that the results are reproducible and accuracy in the method used to prepare the patches.

***In-vitro* residence time of patches**

The in *vitro* residence time was determined by employing a modified USP disintegration apparatus. The average *In-vitro* residence time of all patches was given in Table 9.14.

The in *vitro* residence time of formulation F1, F2 and F3 composed of polymers such as sodium alginate and HPMC in various ratios were about 3.43±0.12**,** 3.16±0.12 and 3.49±0.09 hrs respectively. The in *vitro* residence time of formulation F4 and F5 composed of polymers such as sodium alginate and carbapol 934 in various ratios were about 4.24±0.13 and 4.11±0.05 hrs respectively. The in *vitro* residence time of formulation F6 and F7 composed of polymers such as sodium alginate, HPMC and carbapol 934 in various ratios were about 6.47±0.15 and 7.15±0.13 hrs respectively**.** The in *vitro* residence time of formulation F8 and F9 composed of polymers such as sodium alginate, HPMC and NaCMC in various ratios were about 5.24±0.11 and 5.34±0.12 hrs respectively**.**

In vitro residence time for various patches prepared was in the range of 3.16±0.12 to 7.15±0.13 hr depending on the mucoadhesion properties of the polymer used. This increased residence time that was mainly due to the strong mucoadhesive property of the Carbopol.

Table-9.14 Data of *in vitro* residence time and drug content uniformity

Formulations	*In Vitro* Residence time (Hrs)	Drug Content Uniformity %
F1	3.43±0.12	93.38± 0.27
F2	3.16±0.12	90.14 ± 0.07
F3	3.49±0.09	92.36 ± 0.11
F4	4.24±0.13	94.01± 0.40
F5	4.11±0.05	91.27 ± 0.49
F6	6.47±0.15	96.79± 0.07
F7	7.15±0.13	98.75 ± 0.80
F8	5.24±0.11	92.95 ± 0.11
F9	5.34±0.12	96. 88± 0.81

*All values are expressed as mean± S.D., n=3

Table-9.15: Datas of *Ex-vivo* permeation release studies of Tramadol HCl loaded mucoadhesive buccal patches

Time in hrs	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	17.68±1.12	15.06±0.57	16.20±0.72	16.20±0.82	18.01±0.18	18.50±1.12	20.30±1.82	18.01±0.87	18.50±1.02
1	22.05±0.15	21.18±1.62	21.93±0.16	21.93±0.10	24.70±0.67	26.87±0.10	25.70±0.10	23.55±1.12	24.90±0.57
1.5	28.78±0.60	27.37±1.10	28.83±0.10	27.85±0.17	30.99±0.34	32.68±0.19	34.36±0.12	31.06±0.02	29.07±0.62
2	36.26±1.72	34.59±0.52	34.51±1.52	35.91±0.82	38.13±0.12	40.26±1.62	41.58±1.10	38.05±0.92	36.54±1.12
3	42.36±1.10	40.26±0.10	39.99±0.40	41.83±1.12	42.87±1.12	43.50±0.92	48.52±0.19	43.12±0.12	41.50±1.72
4	48.91±0.19	45.53±1.18	46.86±1.32	46.06±0.10	47.62±1.22	49.32±0.10	59.24±0.49	48.88±0.87	46.97±0.56
5	59.05±0.13	56.92±1.12	57.03±1.12	56.48±0.85	58.10±0.14	61.32±0.12	65.32±0.95	55.69±1.10	54.31±1.19
6	64.99±1.12	63.58±1.02	63.51±1.19	62.74±1.02	66.40±0.18	68.18±0.14	70.92±1.92	62.32±1.02	61.02±0.92
7	66.10±0.60	65.50±0.17	64.88±1.15	64.23±1.02	68.12±0.45	71.64±0.92	75.21±0.42	68.71±1.42	66.53±0.12

*All values are expressed as mean± S.D., n=3

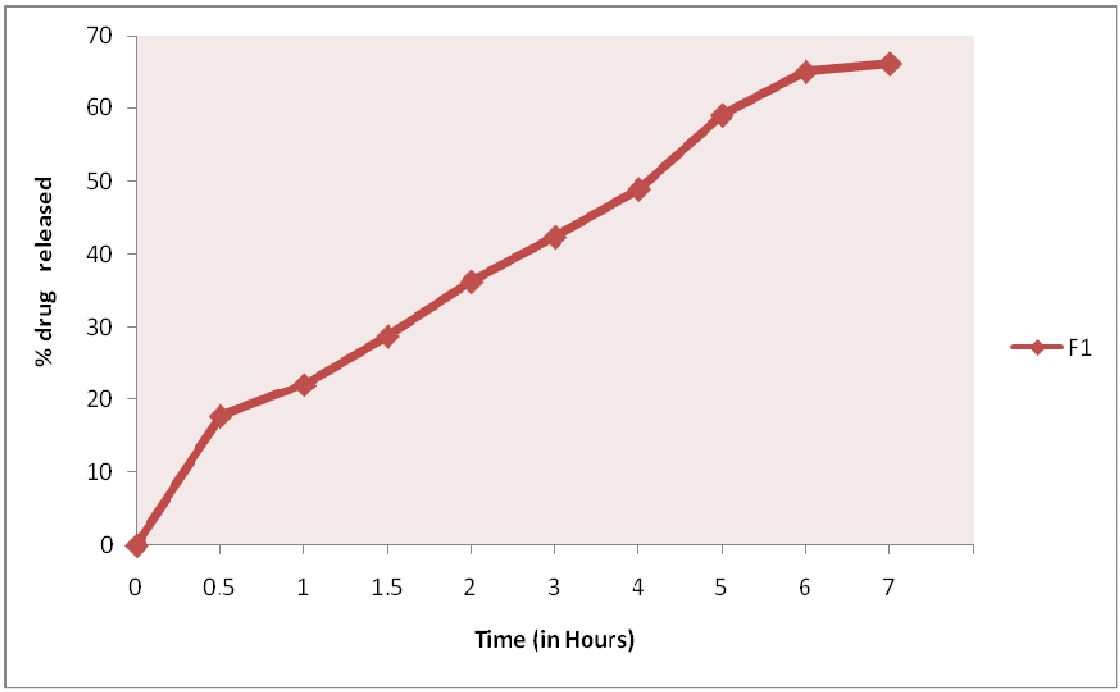


Figure-9.19 Diffusion profile of formulation F1

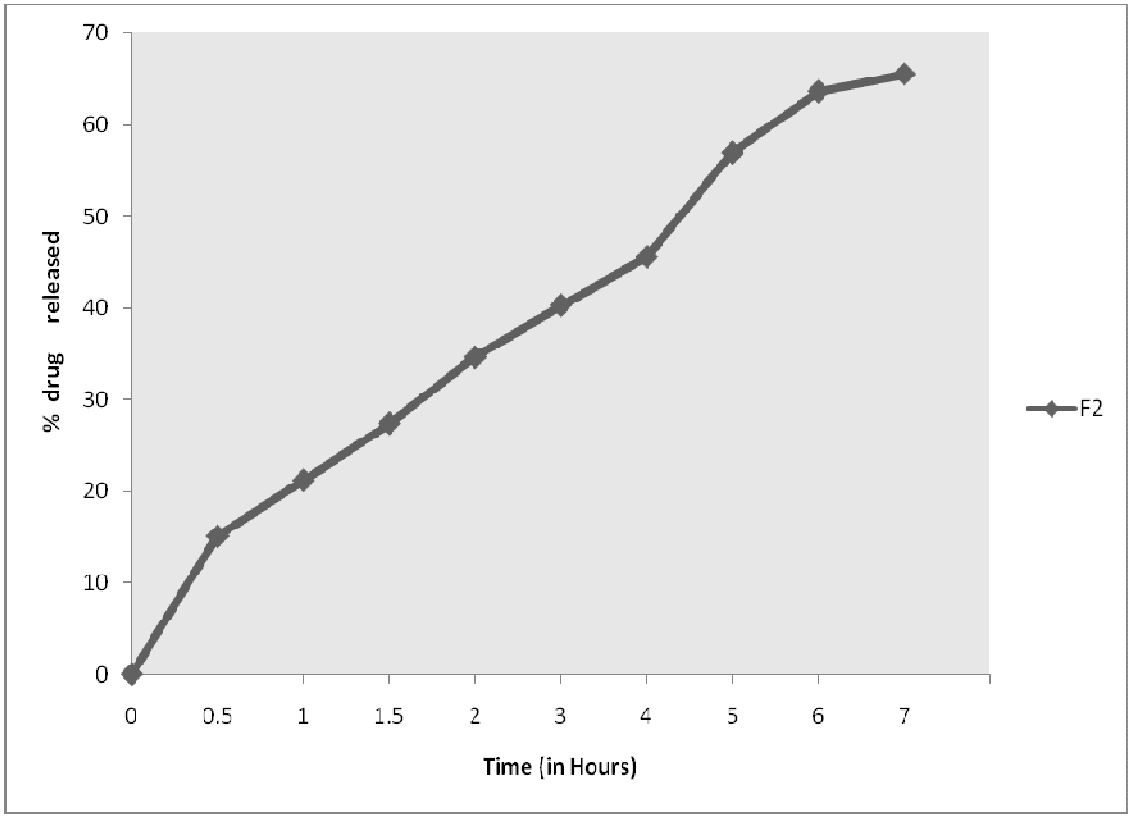


Figure-9.20 Diffusion profile of formulation F2

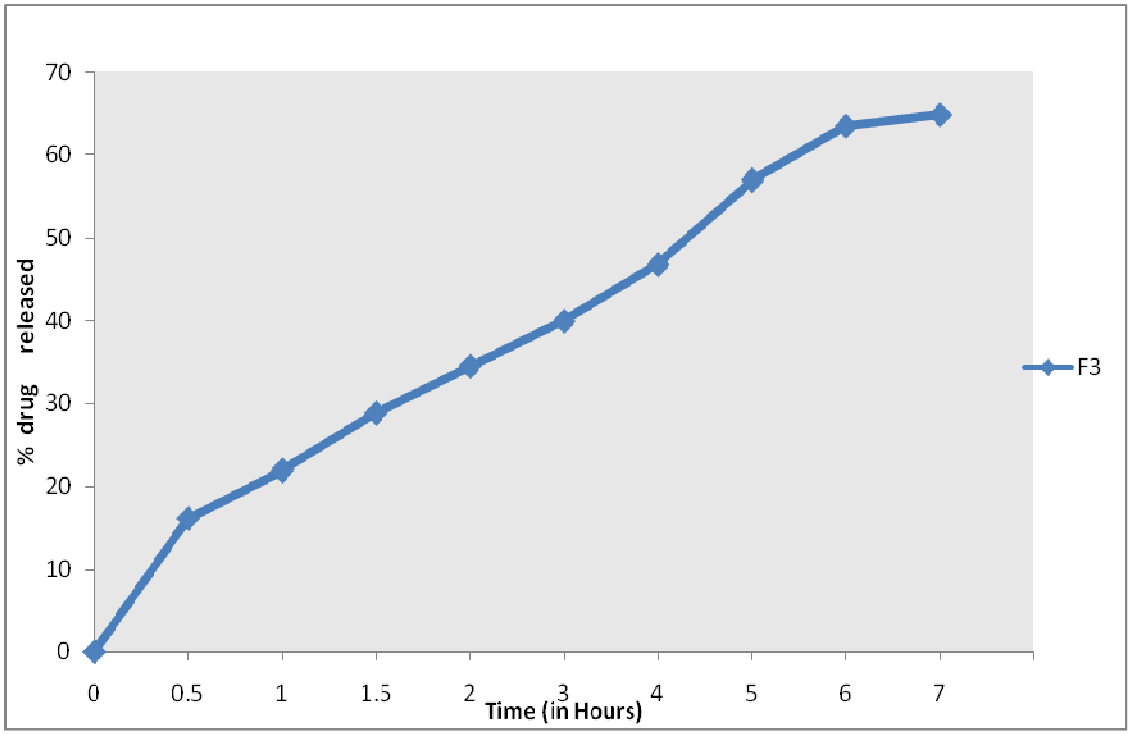


Figure-9.21 Diffusion profile of formulation F3

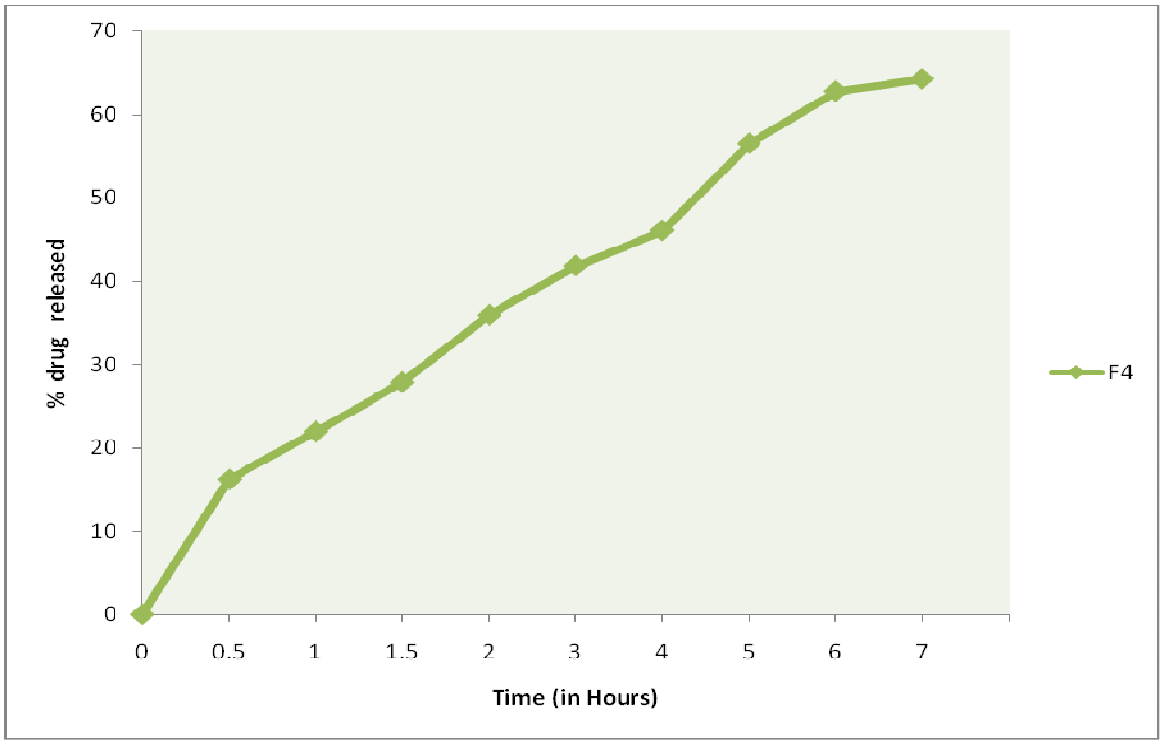


Figure-9.22 Diffusion profile of formulation F4

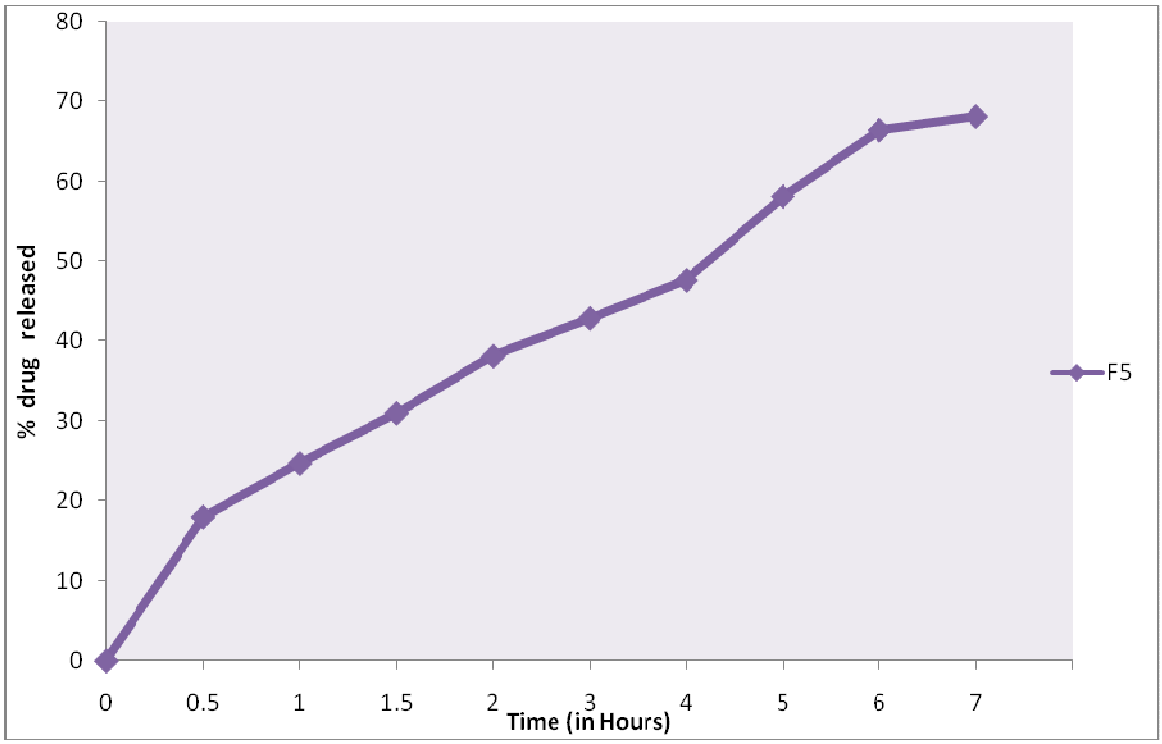


Figure-9.23 Diffusion profile of formulation F5

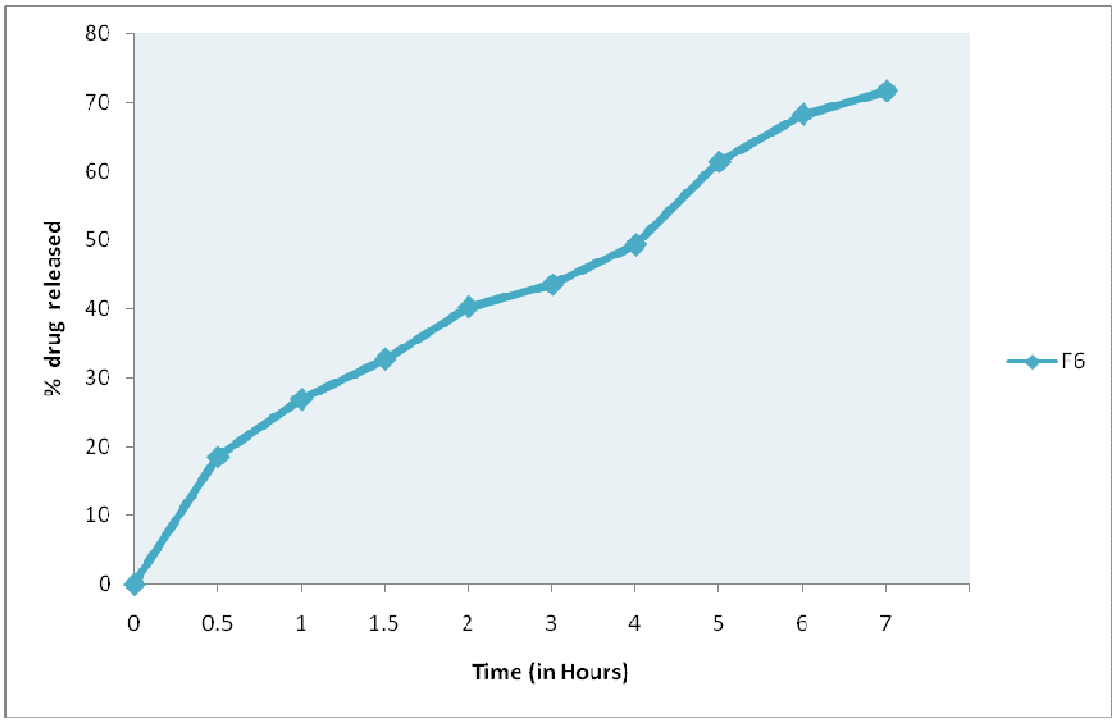


Figure-9.24 Diffusion profile of formulation F6

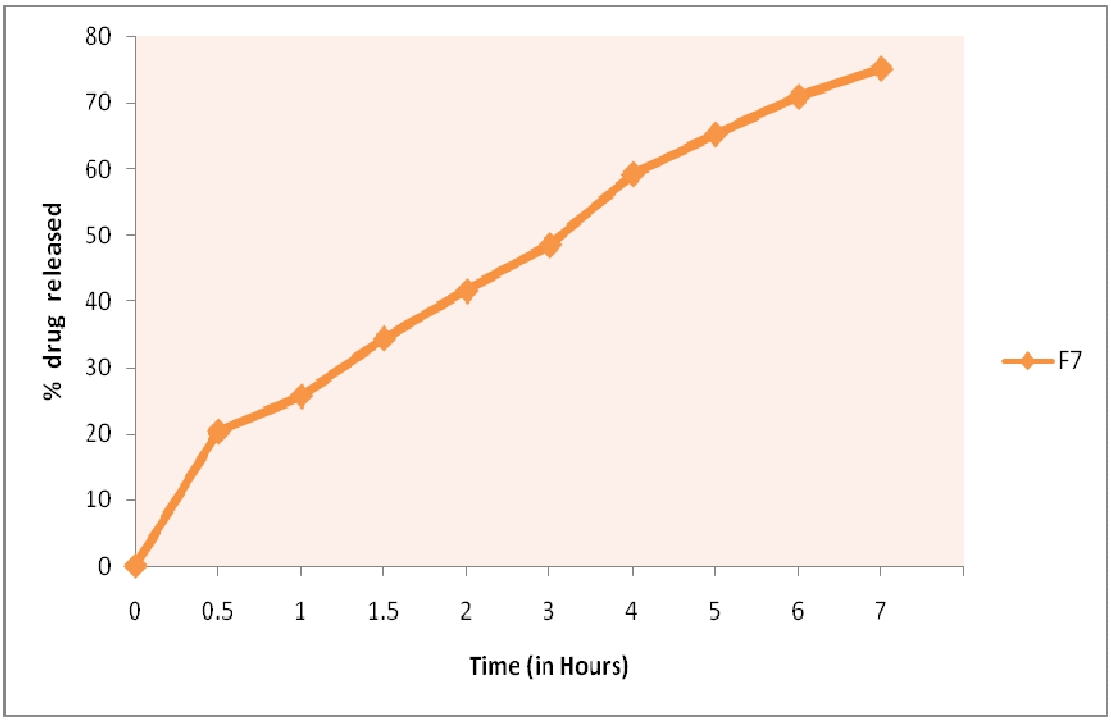


Figure-9.25 Diffusion profile of formulation F7

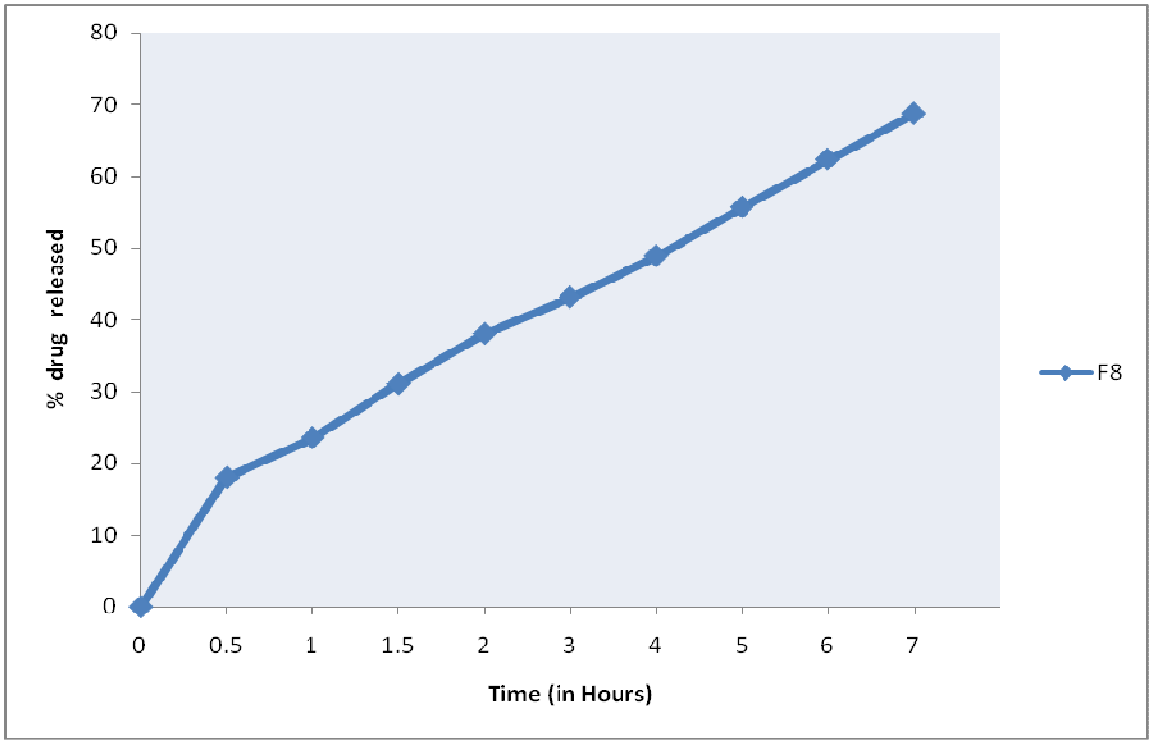


Figure-9.26 Diffusion profile of formulation F8

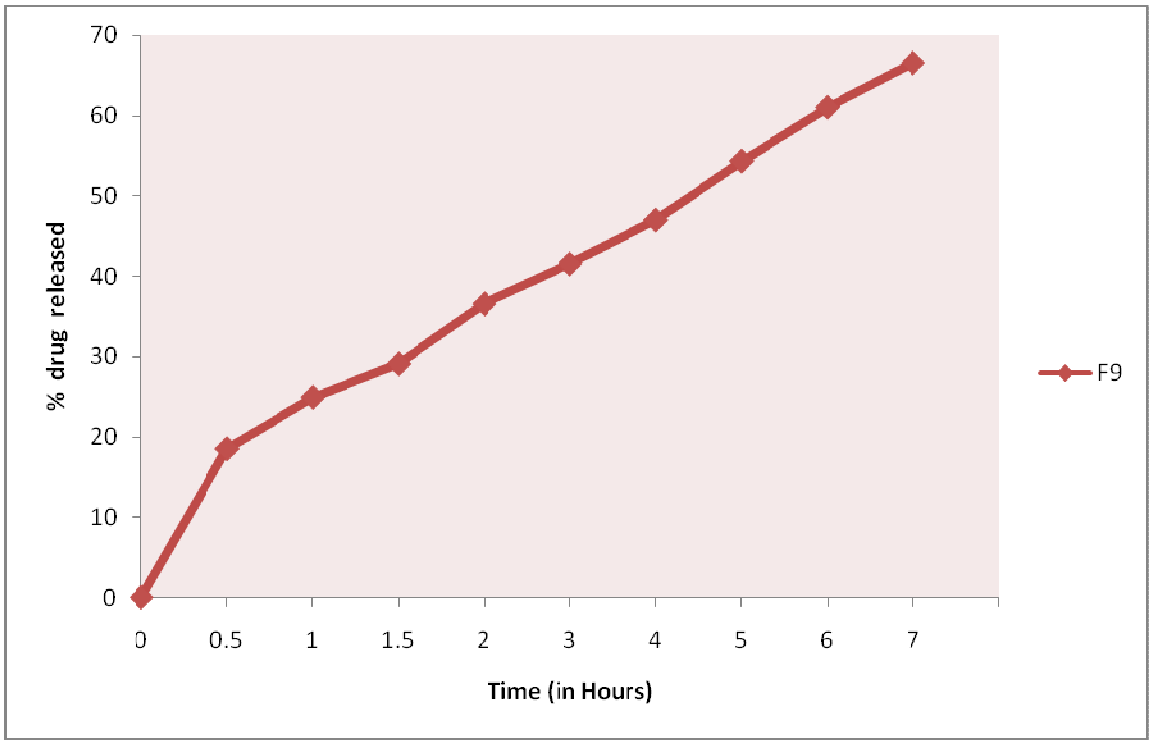


Figure-9.27 Diffusion profile of formulation F9

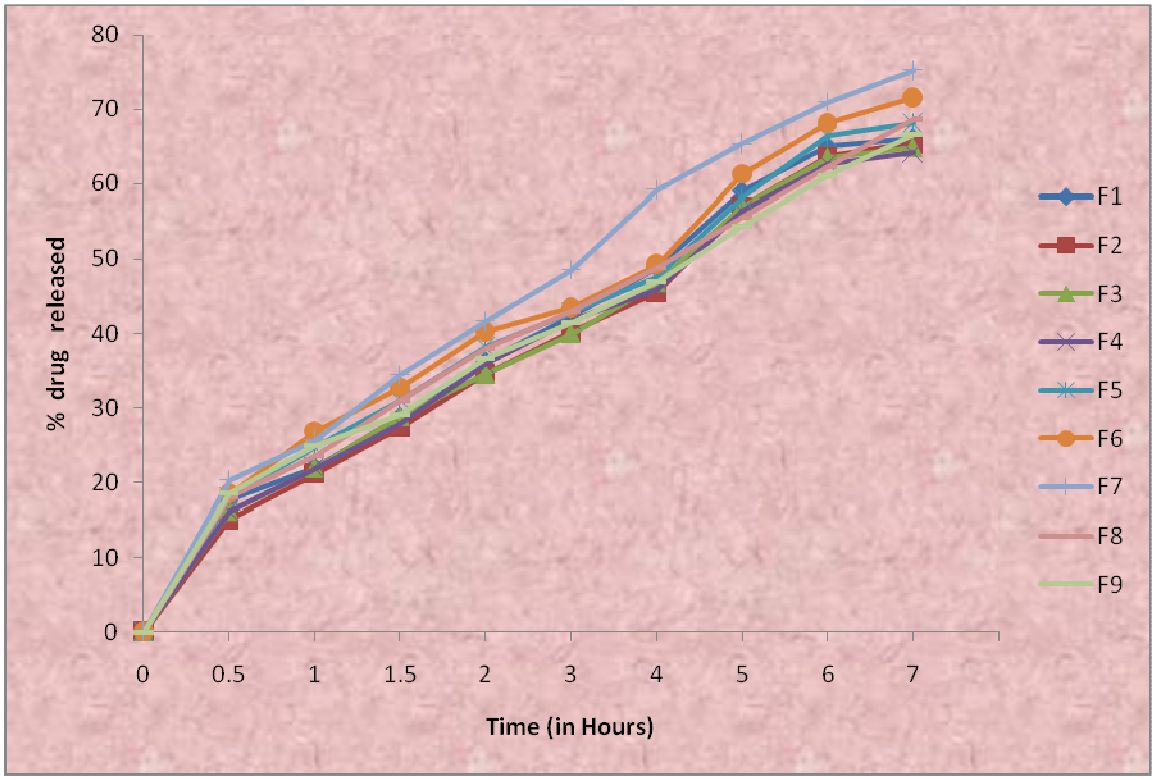


Figure-9.28 Comprehensive diffusion profile of formulation F1-F9

The *Ex-vivo* permeation from buccal patches varied with respect to the polymer composition and nature. An increase in drug release from the buccal patches was found with increasing concentration of polymers that were more hydrophilic in nature. Among all formulations, the formulation F7 was shown maximum Ex-*vivo* permeation **(75.21 ± 0.42%)** over a period of 7 hrs were observed .All the data of diffusion profiles were represented in table 9.15 and shown graphically in figure 9.19 to 9.28.

Table 9.16 Data of *in vitro* release profile of Tramadol HCl loaded mucoadhesive buccal patches

Time in hrs	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	22.18±1.12	24.84±1.34	22.18±0.49	22.81±1.52	23.75±0.94	26.71±1.82	25.15±1.12	21.71±0.18	23.43±0.56
1	27.34±0.12	30.46±1.12	29.18±0.15	28.90±0.62	30.93±0.67	34.68±1.12	36.71±1.22	29.37±0.19	28.9±1.12
1.5	35.15±0.42	37.34±0.82	34.06±1.02	37.18±0.42	38.59±1.32	41.71±0.52	44.53±1.22	37.65±0.60	35.93±1.22
2	42.03±0.32	43.59±0.12	40.78±0.54	43.28±1.72	44.37±1.42	49.84±0.90	50.78±0.42	44.53±1.52	42.3±0.14
3	53.43±1.12	55.15±1.12	49.78±0.70	51.56±1.12	53.43±1.10	56.71±1.14	57.96±0.62	53.25±0.56	49.53±0.22
4	61.71±1.42	63.28±1.18	57.96±0.50	64.37±0.10	66.09±0.70	68.43±0.82	69.53±0.70	60.46±0.19	58.12±1.32
5	67.34±0.52	67.18±0.68	64.84±1.14	67.34±0.68	68.75±0.92	73.59±0.72	74.21±1.12	70.62±0.16	65.15±1.42
6	72.34±0.92	69.37±0.50	68.15±1.18	70.15±0.82	71.87±0.14	75.46±0.23	78.43±0.42	75.93±0.72	72.03±0.98
7	74.27±1.16	71.71±1.14	70.78±1.02	71.10±1.52	73.43±0.13	77.50±1.22	82.03±0.82	78.28±1.22	75.78±0.18

*All values are expressed as mean± S.D., n=3

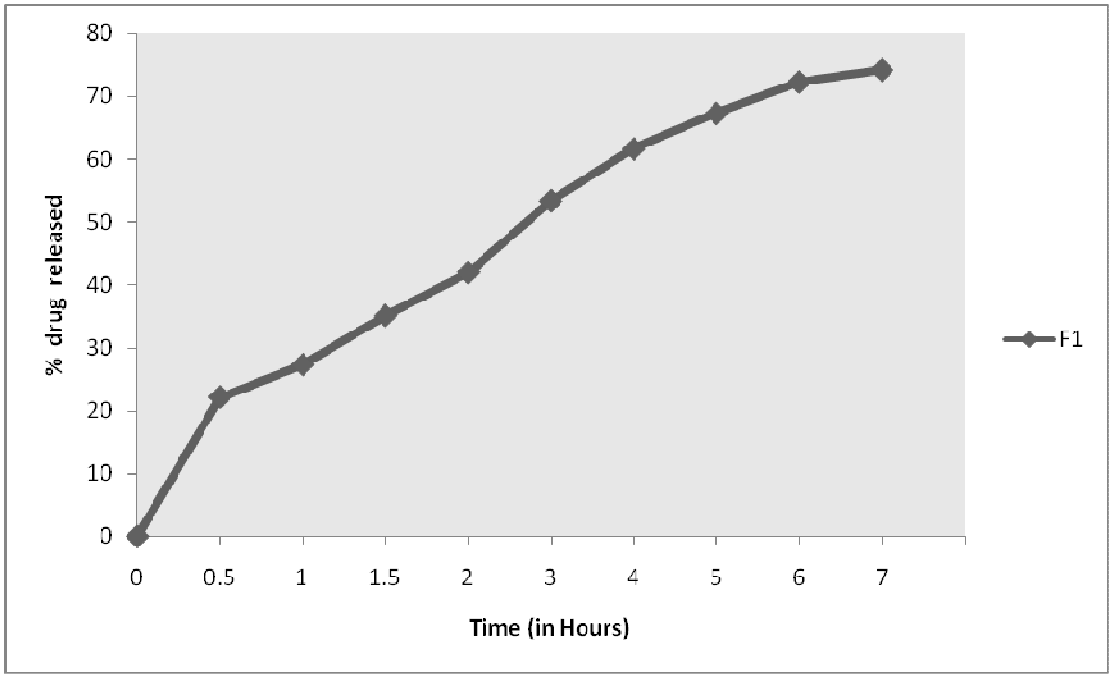


Figure-9.29 *In-vitro* release profile of formulation F1

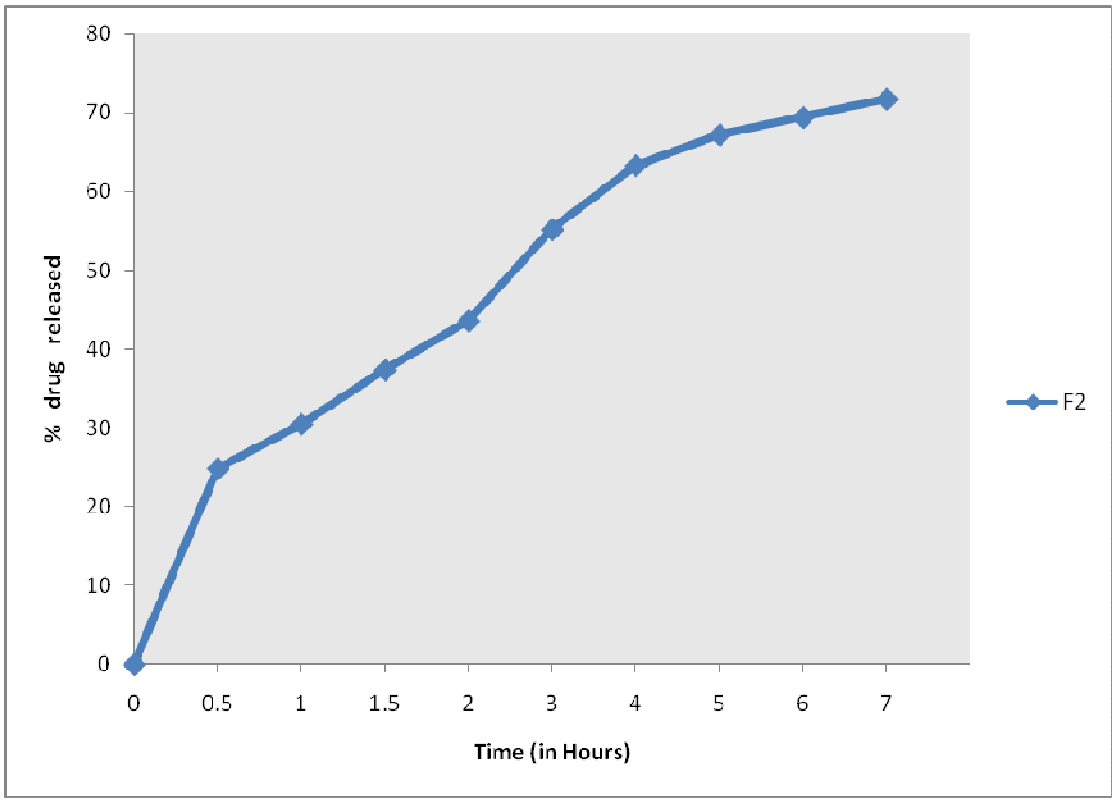


Figure-9.30 *In-vitro* release profile of formulation F2

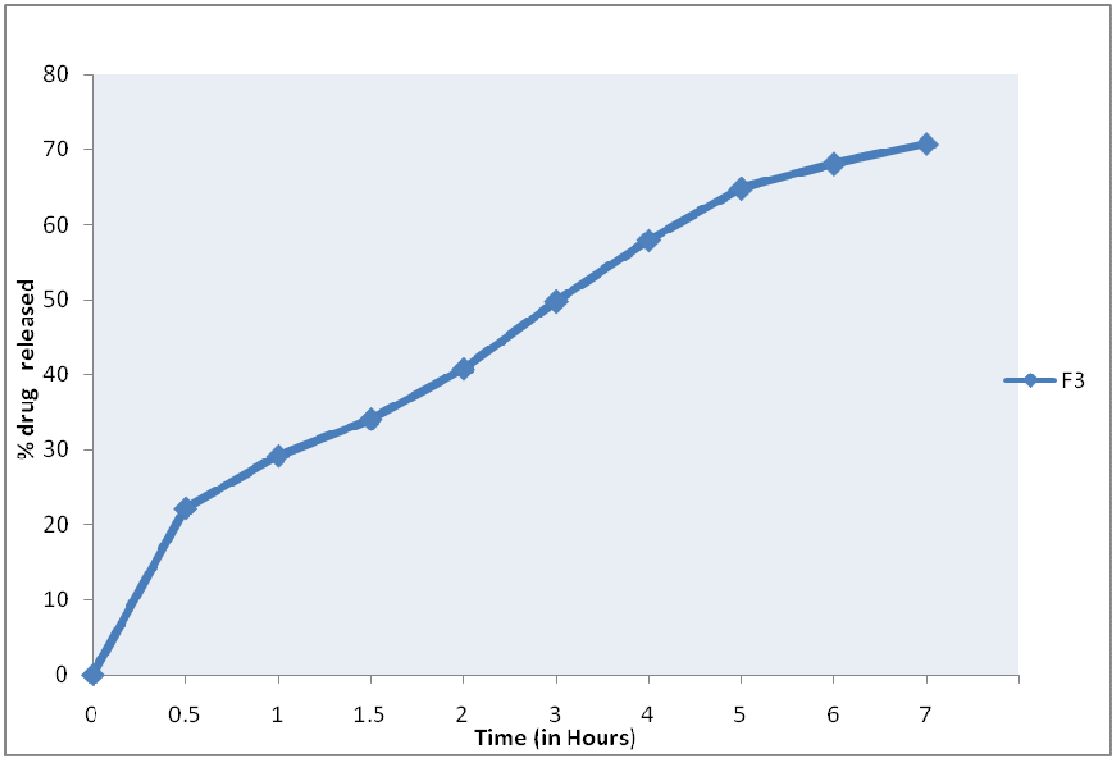


Figure-9.31 *In-vitro* release profile of formulation F3

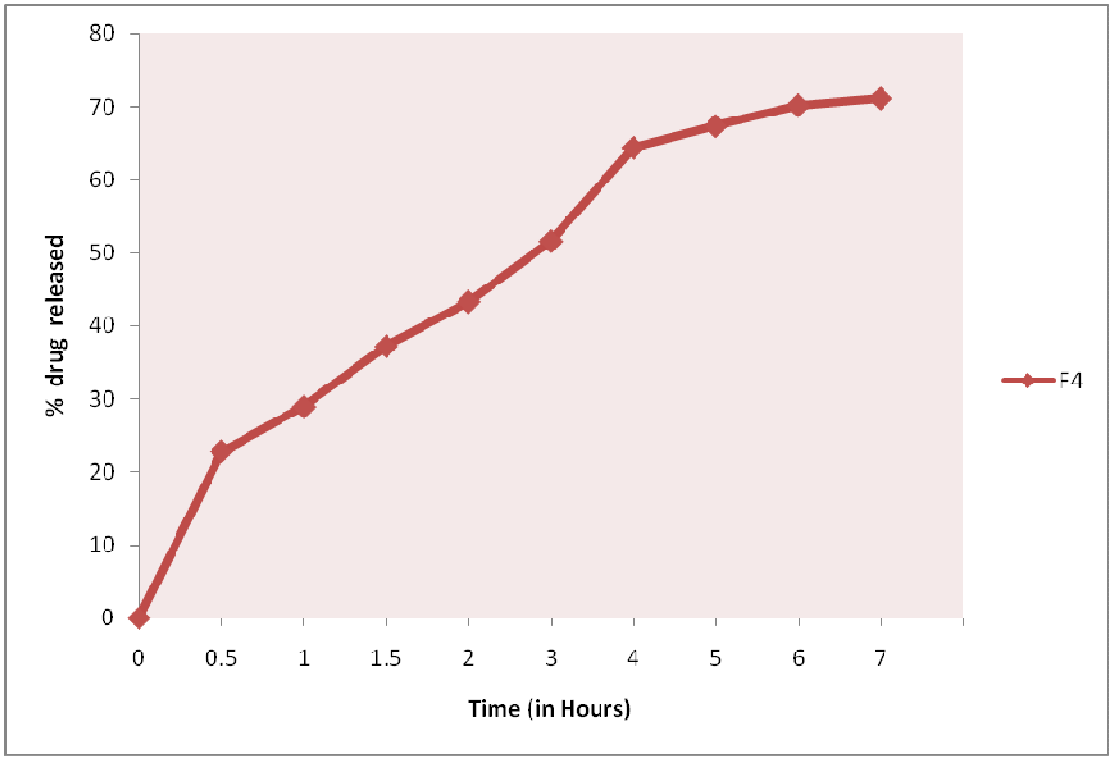


Figure-9.32 *In-vitro* release profile of formulation F4

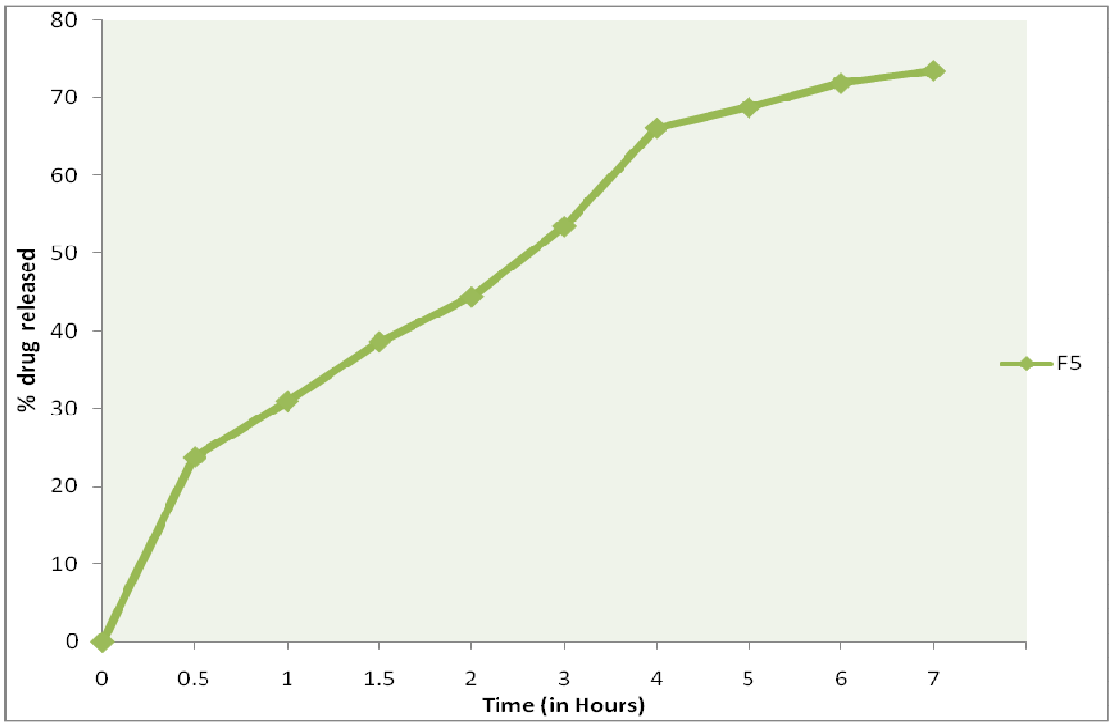


Figure-9.33 *In-vitro* release profile of formulation F5

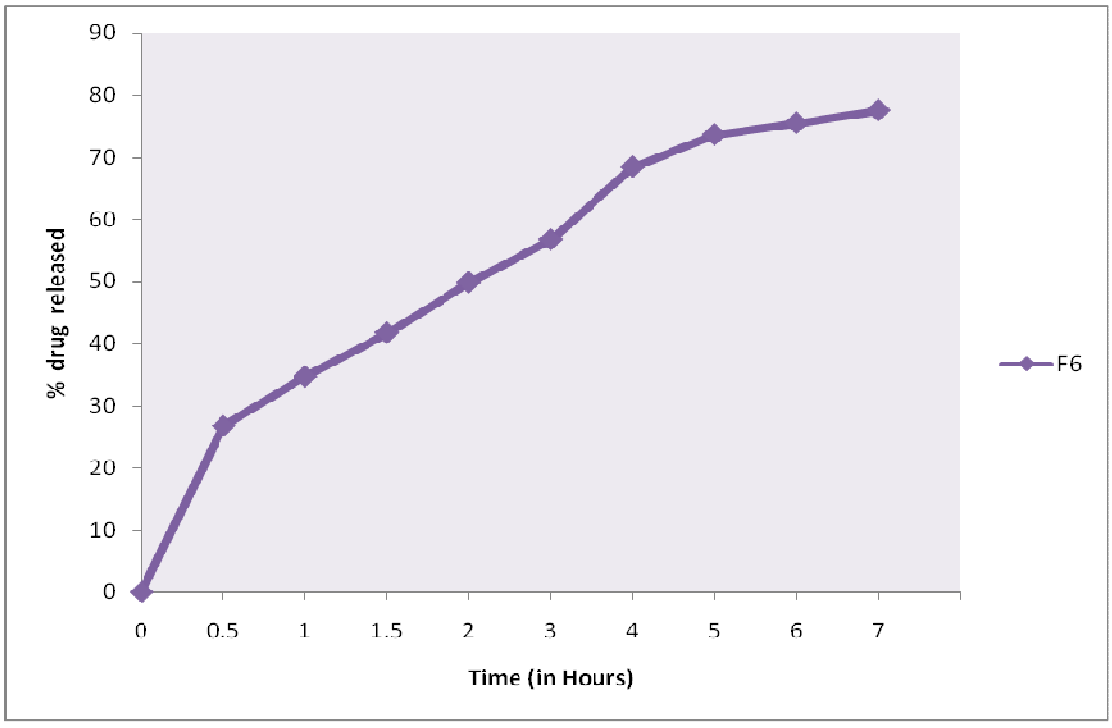


Figure-9.34 *In-vitro* release profile of formulation F6

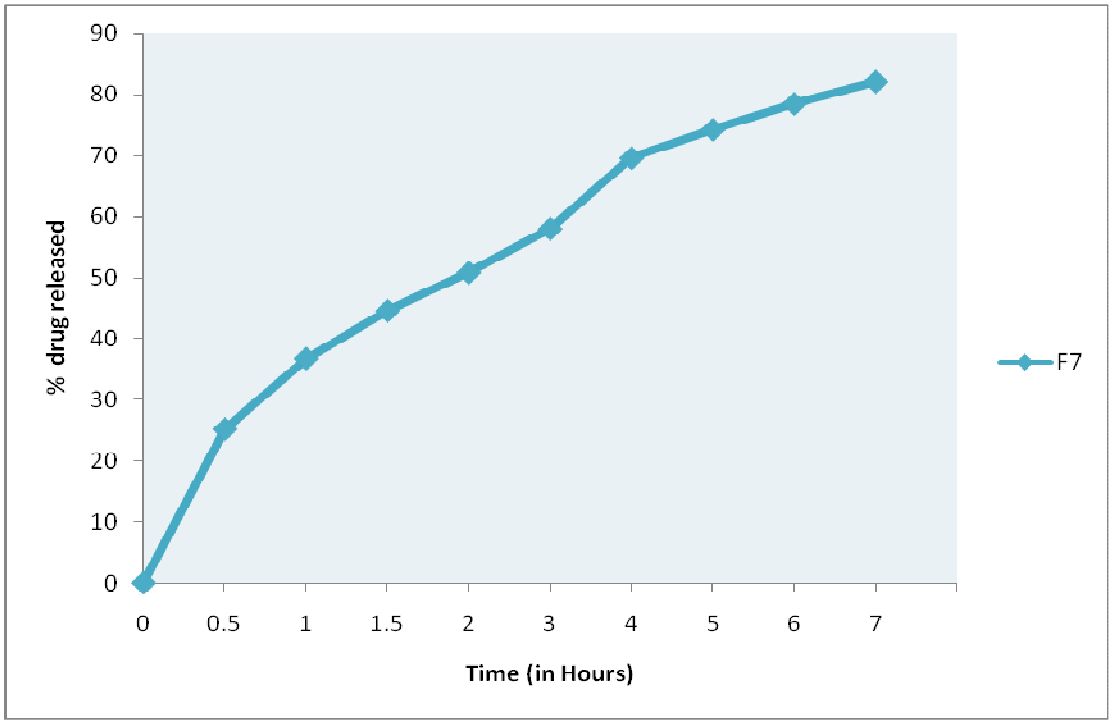


Figure-9.35 *In-vitro* release profile of formulation F7

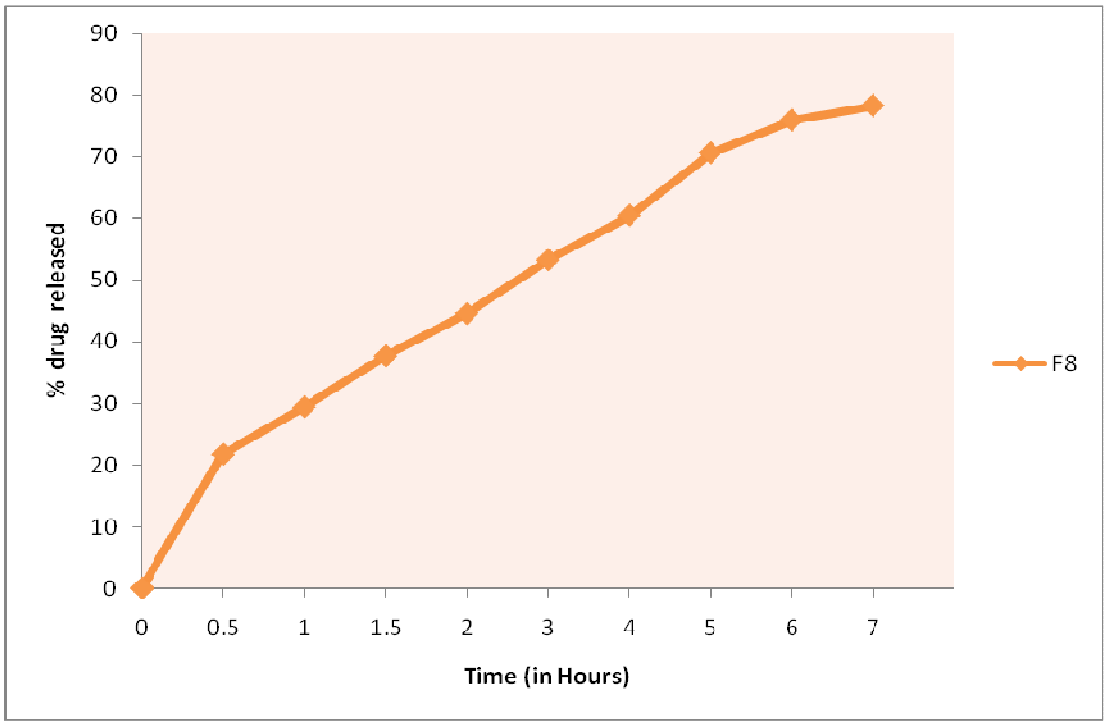


Figure-9.36 *In-vitro* release profile of formulation F8

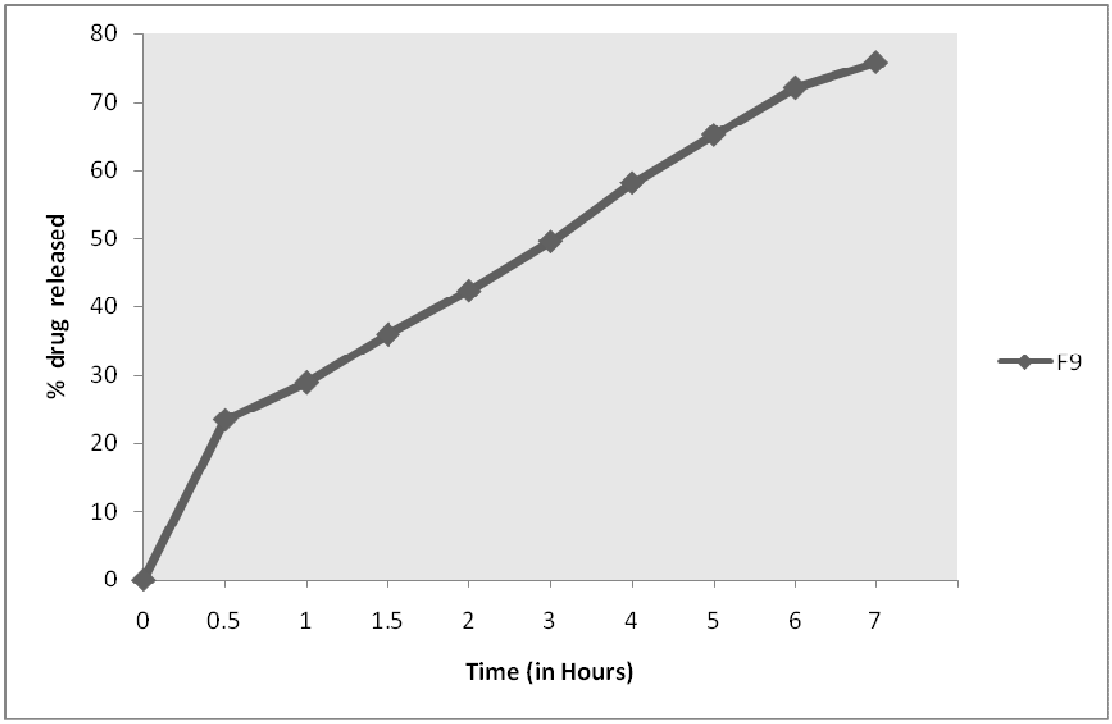


Figure-9.37 *In-vitro* release profile of formulation F9

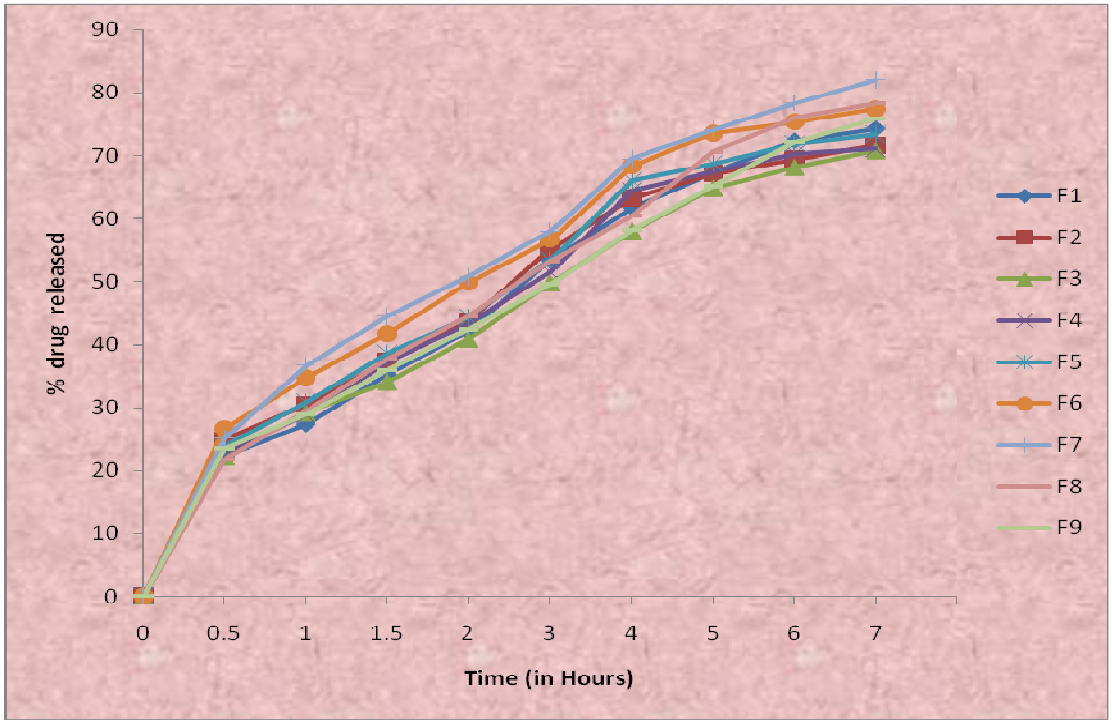


Figure-9.38 comprehensive *In-vitro* release profile of formulations F1-F9

The data of *in- vitro* drug release profile from buccal patches varied with respect to the polymer composition and nature. An increase in drug release from the buccal patches was found with increasing concentration of polymers that were more hydrophilic in nature. Among all formulations, the formulation F7 was shown maximum in-*vitro* drug released (**82.03 ±0.82 %**) over a period of 7 hrs was observed .All the *in-vitro* drug release profiles were represented in table 9.16 and showed in figure 9.29 to 9.38.

9.4.12 Kinetics of Drug release

The kinetics of *In-vitro* drug release was determined by applying the drug released data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas. The results obtained were represented in Table 9.17 and shown in Figure 9.39 to 9.47.

Table 9.17: *In vitro* drug released kinetics studies of all formulations

Formulations	Zero order R^2	First order R^2	Higuchi R^2	Korresmayer Peppas		Best fit model
				R^2	n	
F1	0.992	0.752	0.947	0.995	0.4539	Peppas
F2	0.990	0.766	0.928	0.993	0.4437	Peppas
F3	0.994	0.752	0.925	0.995	0.4002	Peppas
F4	0.989	0.832	0.958	0.993	0.4771	Peppas
F5	0.992	0.894	0.951	0.995	0.4226	Peppas
F6	0.993	0.872	0.928	0.994	0.4588	Peppas
F7	0.993	0.872	0.928	0.999	0.3744	Peppas
F8	0.988	0.841	0.909	0.991	0.3481	Peppas
F9	0.997	0.939	0.930	0.998	0.3475	Peppas

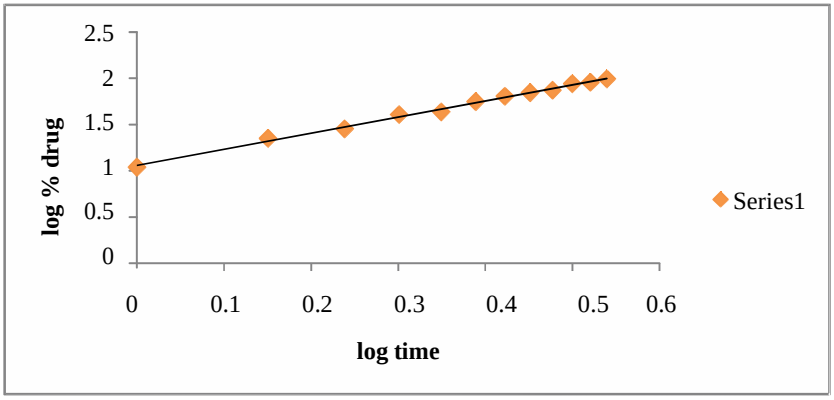


Figure 9.39: The best fit model of formulation F1

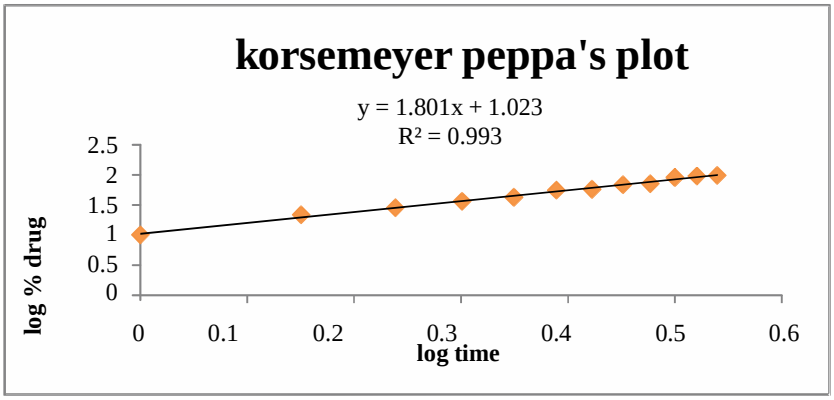


Figure 9.40: The best fit model of formulation F2

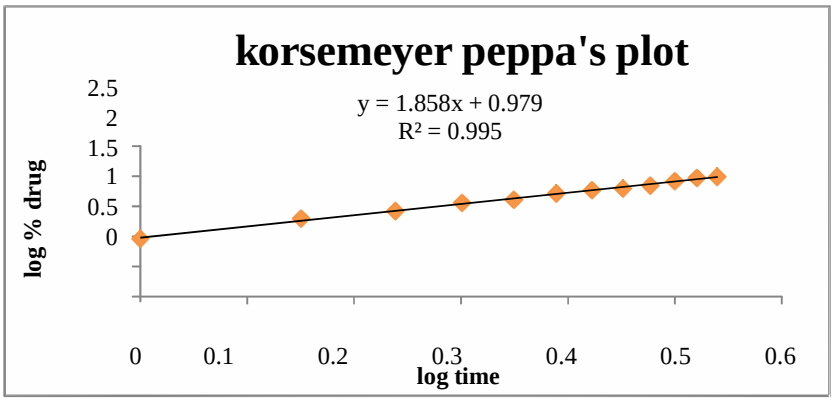


Figure 9.41: The best fit model of formulation F3

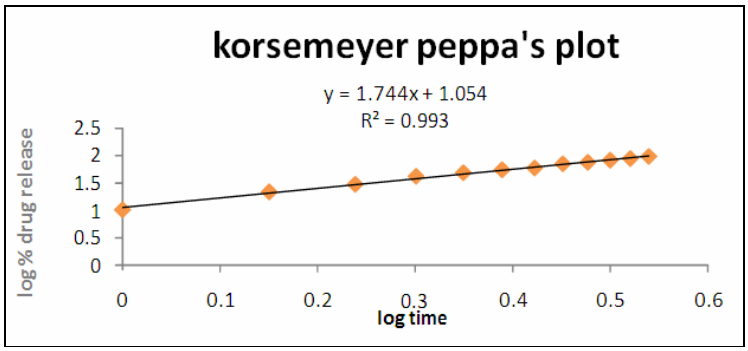


Figure 9.42: The best fit model of formulation F4

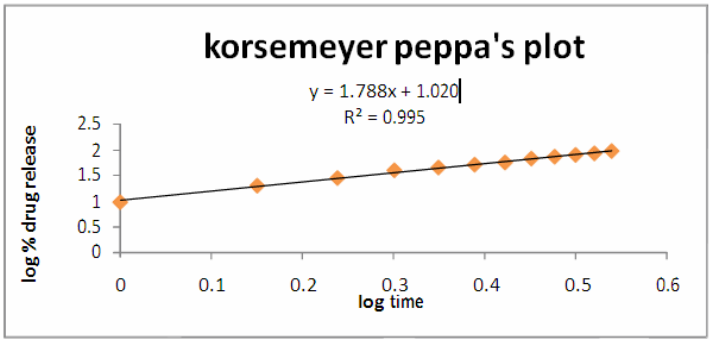


Figure 9.43: The best fit model of formulation F5

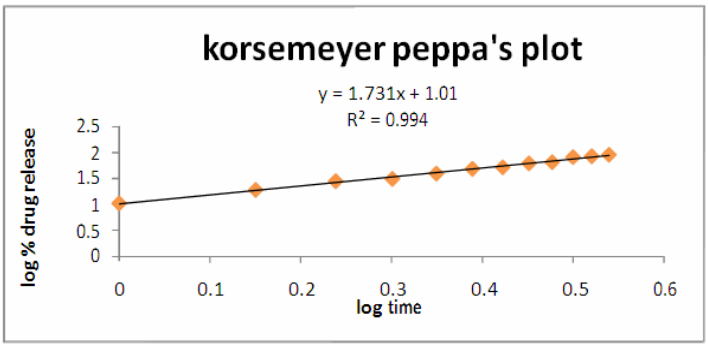


Figure 9.44: The best fit model of formulation F6

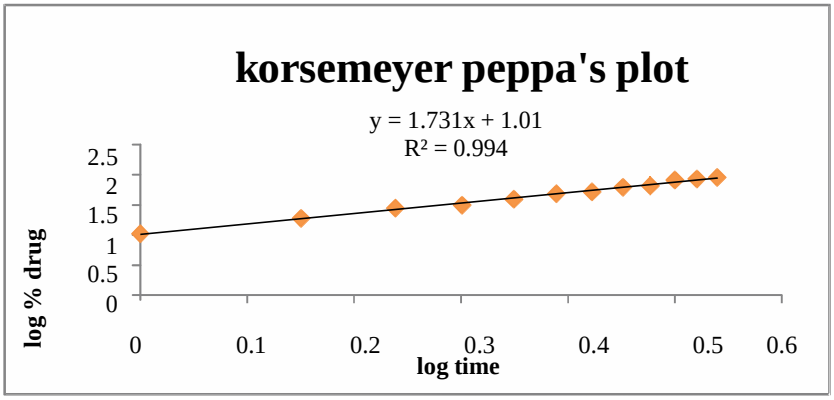


Figure 9.45: The best fit model of formulation F7

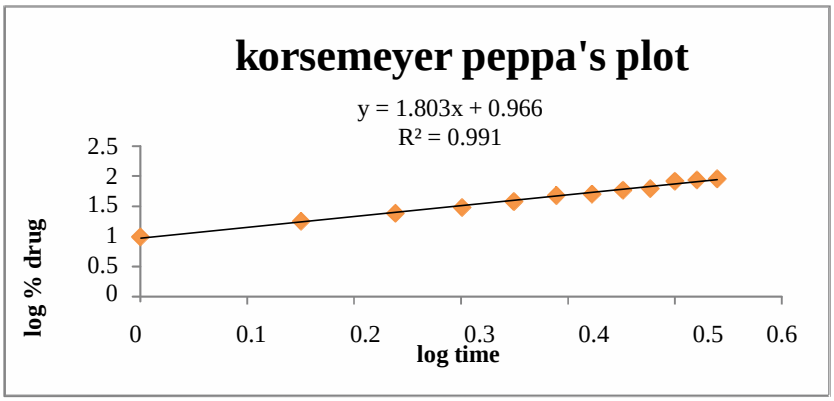


Figure 9.46: The best fit model of formulation F8

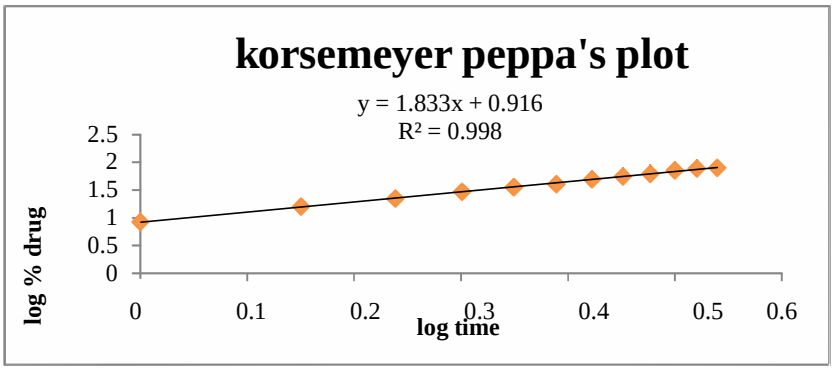


Figure 9.47: The best fit model of formulation F9

The drug released from the mucoadhesive buccal patches was diffusion controlled.

9.4. STABILITY STUDIES

The formulation F7 was further subjected to stability study at specified period in appropriate storage condition as per ICH guidelines .The formulation was monitored for appearance, surface pH, drug content, *In-Vitro* residence time, *In-Vitro* drug released and *Ex-Vivo* peremeation and results were represented in Table 9.18 and shown in figure 9.48.

Table-9.18 Data of stability studies of formulation F7

STABILITY STUDIES	**APPEARANCE**	**SURFACE PH**	**CONTENT UNIFORMITY (%)**	***IN-VITRO* RESIDENCE TIME (HR)**	***IN-VITRO* DRUG RELEASE**	***Ex-VIVO* PEREMEA –TION**
Initial	Smooth surface& elegant texture	6.40±0.26	98.75±0.80	7.15±0.13	82.03±0.82	75.21 ±0.42
First month	Smooth surface& elegant texture	6.29±0.09	98.22±0.20	7.05±0.05	81.86±0.07	75.03 ±0.05
Second month	Smooth surface& elegant texture	6.20±0.01	98.18±0.03	6.45±0.05	81.52±0.08	74.52±0.12
Third month	Smooth surface& elegant texture	6.09±0.03	98.05±0.04	6.27±0.02	80.33±0.06	74.09 ±0.73

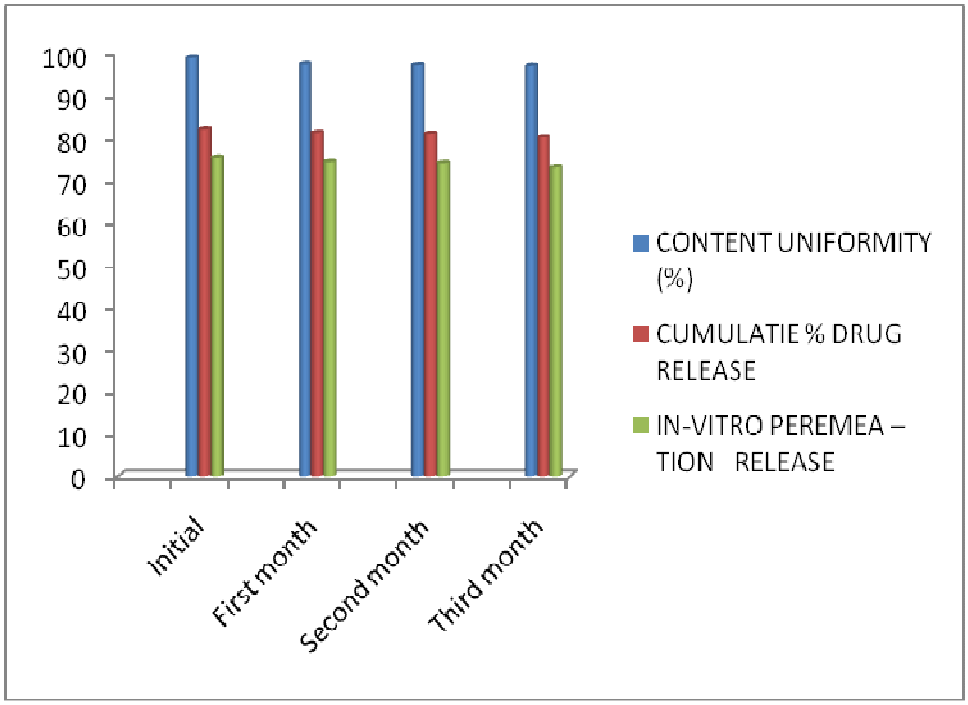


Figure 9.48: Graphical representation of stability data

SUMMARY AND CONCLUSION

10. SUMMARY AND CONCLUSION

- The main goal of the present investigation efforts was to develop and evaluate new buccal patches comprising a drug- containing mucoadhesive polymeric layer using polymers like sodium alginate, sodium carboxy methyl cellouse, Hydroxy propyl methyl cellouse, and Carbopol 934 in various combinations and proportions and a drug-free PVA-aluminum foil backing membrane .
- The prepared patches were evaluated for number of parameters like physical appearance, surface texture, weight uniformity, thickness of patches, folding endurance, surface pH, swelling index, *in vitro* residence time, drug excipient interaction studies, drug uniformity ,*Ex vivo* drug permeation and *in vitro* drug release.
- The patches prepared were checked visually for its appearance & surface texture. All the prepared patches were of smooth surface & elegant texture.
- All the prepared patches using different concentration of various polymers were weighing in between 25 ±1.73 to 47.66 ±0.57 mg.
- The patches showed folding endurance values in between 238.0 ±1.95 to 293.33 ±2.64.
- The evaluated patches showed high swelling index values 0f about 25.01% after 7hr in the case of formulation F7 due to the high swelling property of the polymer carbopol 934. Similarly surface pH of all the patches prepared was ranging in between 5.76±0.11 & 6.46±0.05pH.
- *In vitro* residence time for various patches prepared was in the range of

3.16±0.12 to 7.15±0.13 hr depending on the mucoadhesion properties of the polymer used. This increased residence time that was mainly due to the strong mucoadhesive property of the Carbopol.

- The Fourier transform Infra-Red (FTIR) and Differential scanning calorimetry (DSC) studies indicate that Tramadol hydrochloride showed complete entrapment within the polymer carrier bonding is suggested and there were no chemical interaction.
- Similarly, the patches were also estimated to drug content uniformity study and it lies in between 90.14± 0.07 & 98.75 ± 0.80 % which suggest that uniform dispersion throughout the buccal patches.
- The *in- vitro* drug release and *Ex-vivo* permeation from buccal patches varied with respect to the polymer composition and nature. An increase in drug release from the buccal patches was found with increasing concentration of polymers that were more hydrophilic in nature. The formulation F7 was shown best one among the formulations (F1 to F9) were prepared. Formulation F7 *in-vitro* drug released was 82.03 ±0.82 % and *Ex-vivo* permeation was 75.21 ± 0.42% over a period of 7 hrs was observed.
- The data of *in-vitro* release where fit in kinetic models . The kinetic models used were zero order equation, first-order equation, higuchi release and peppas model. The best fit with highest correlation coefficient (r) was shown by korsmeyer and Peppas **(r=0.999)**. "n" value of all the formulation was less than 0.5,it shows that the formulation F7 was follows Fickian model of drug release.
- Form the stability data it can be concluded there was no significant change in appearance, surface pH, content uniformity, *in-vitro* residence time and *in-*

vitro drug release, *Ex-vivo* peremeation release. Hence the formulation F7 was stable formulation.

- The overall studies concluded that the formulation F7 was composed of Tramadol HCl(50mg), sodium alginate (700 mg), HPMC (100 mg) and carbopol 934 (200 mg) showed satisfactory and better release profile. Hence the formulation F7 selected as best formulation.

FUTURE PROSPECTS

11. FUTURE PROSPECTS

In this present work, physio-chemical characterization and *in vitro* evaluation of Taramdol HCl loaded mucoadhesive buccal patches were performed.

In future *in-vivo* studies will be conducted to set *in-vitro in-vivo* correlation which is necessary for the successful formulation development.

In future the long term stability studies are required to know the shelf life of the prepared buccal patches.

The various formulations will be developed with Taramdol HCl using other polymer and plasticizers in future.

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